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**FUNDAMENTAL CONCEPTS IN ENDOCRINE DIAGNOSIS
AND THERAPY**

EDWIN J. KEPLER AND LAWRENCE M. RANDALL*

The present status of endocrinology.—The youth of endocrinology as a specialized division of medicine is attested by the fact that even such basic terms as "hormone" and "endocrine" did not appear in medical literature until the beginning of the present century. Since then endocrinology has become one of the most rapidly growing of all the specialties. Entire laboratories have devoted all their resources to the investigation of endocrine problems (especially those centering about the pituitary body, adrenal glands and the gonads), and journals have been given over to the publication of their results. Growth not only has been rapid but asymmetric. Clinicians have been unable to follow the pace set by the workers in research. For example, in one of the recent issues of a journal devoted exclusively to endocrinologic matters, less than one-fifth of the space was assigned to clinical papers. Not only has the field been dominated by experimentalists but, as so often is the case with a rapidly growing branch of science, results have not always been either *conclusive* or *mutually compatible*.

It should not be inferred from the foregoing remarks that endocrinology is not making genuine advances. Some of the recent discoveries will rank among the great medical achievements of all time. The biochemists, in particular, have been forging ahead. From the thyroid gland, the adrenal cortex and medulla, the islets of Langerhans and the gonads, they

* With the assistance of the other contributors to this symposium.

have extracted crystalline substances that provide the means for replacement therapy of a high degree of effectiveness. The chemical formulas of many of these compounds have been ascertained and in some instances synthesis has been accomplished. In the case of the parathyroid glands and the posterior lobe of the pituitary body, extracts have been prepared which can be used clinically. Only the extracts of the anterior lobe of the pituitary body are still crude and on the whole unsatisfactory for clinical use, and there seems little likelihood that good preparations will be available in the near future.

As new substances were prepared, new terms became necessary. Some of the terms proved to be unsatisfactory and were subsequently dropped or modified; others that did survive were so cumbersome that they had to be abbreviated. Endocrinologic literature therefore became difficult to read. This fact, in conjunction with the inherent intricacies of the subject matter and the limited critique of the profession when dealing with innovations, has made self-education in endocrinologic matters a particularly difficult problem for most physicians.

Another of the several consequences of the present state of affairs has been that even the well-informed practitioner often approaches his diagnostic endocrine problems with a sense of inferiority and views his therapeutic achievements with a feeling of frustration. There has developed, therefore, a demand for a simple, concise and authoritative synopsis of endocrinology which will enable the physician without specialized training to treat his endocrine patients at least rationally, if not always successfully. Unfortunately, there are no authorities, the subject is still complex, knowledge is limited, and treatment is often unsatisfactory. Probably at least another decade will elapse before the totality of endocrine therapy attains the satisfactory status that now is obtained, for example, in the treatment of myxedema.

Need for accurate diagnosis.—The old adage that effective therapy is based on accurate diagnosis is particularly applicable to modern endocrinology. Fifteen years ago, when with the exception of desiccated thyroid or thyroxin, insulin, adrenalin (epinephrine hydrochloride), and pituitrin, the only

available endocrine preparations were relatively inert mixtures that accomplished little except to deplete the patient's pocket-book, the consequences of injudicious therapy often were not particularly serious. This situation no longer exists. "Organotherapy" has been displaced by "chemotherapy." Hormonal compounds whose dosage is measured in milligrams are on the market. Their therapeutic potentialities are almost equalled by their capacity to do harm. It has become imperative that the physician who prescribes these substances make an accurate diagnosis, and that he have a clear conception of their pharmaceutic effects, their indications and their therapeutic limitations.

In the ensuing series of papers it will be noticed that in some instances the question of *therapy* has been given scant attention. The omission has been deliberate, because there are a number of endocrine diseases that are very poorly understood and for which there is no satisfactory treatment. When dealing with such conditions we have felt that it is more important that the physician appreciate the limitations of what is known rather than that he be encouraged to institute uncertain or worthless treatment. Experimental therapeutics had best be left in the hands of the experimentalists. There are also certain conditions in which there is no unanimity of opinion regarding the merits of several therapeutic procedures. In such instances it is now manifestly impossible to present in didactic form the best method. Finally, there remains a number of diseases that have been studied carefully over long periods. Here medical opinion has had a chance to crystallize and therapy has been fairly well standardized and stereotyped. In dealing with this group of diseases we have felt that we were justified in stressing therapy at the expense of physiologic and diagnostic considerations.

Before proceeding with a discussion of the diseases of the individual ductless glands we feel that some attention should be given to certain general principles that seem to apply to the endocrine system as a whole. These principles may have to be modified or discarded in the future, and they do not necessarily apply with equal force to each member of the system. Nevertheless, irrespective of their ultimate worth, for the time being they do serve to correlate a vast amount of physiologic and

clinical factual material that is otherwise detached and meaningless.

Hormones.—In many respects the glands of internal secretion are similar to chemical manufacturing plants. Raw chemical materials are brought to the glands, new compounds are manufactured, and these in turn are transported elsewhere for use. These new compounds are known as "hormones," which is a term that is derived from the Greek and means "I rouse to activity." Hormones have the property of setting up definite and specific types of physiologic activity in cells or receptors which have the capacity* to respond to the presence of the hormone. Some hormones seem to influence the activity of most, if not all, of the cells of the body; the effects that are produced by others are limited to certain organs or even to certain cells within an organ. In the main there are two types of hormones that are synthesized by the ductless glands:

1. Hormones of the *first type* influence primarily intracellular and extracellular chemical reactions and thereby serve to keep the chemical interchanges of the body constant within physiologic limits. *Thyroxin* is a good example of such a hormone. In the absence of thyroxin, the utilization of oxygen by the cells decreases, and the production of heat by the body under basal conditions is diminished by about 40 per cent. The decreased ability of the cells to use oxygen at the normal rate produces in turn a wide variety of interesting side effects, the end result of which in man is the reduction of life to a mere vegetative existence. It is important to notice that chemical interchanges involving oxygen do continue, but that such interchanges are no longer within the prescribed limits that are essential to health.

2. Hormones of the *second type* co-ordinate the function of certain cells and organs with other organs or with the needs and activities of the organism as a whole. In this group belong, for example, the secretory products of the *gonads* and the *anterior lobe* of the *pituitary*. The response of the female breast to hormonal influences that are present during pregnancy and lactation exemplifies the co-ordination of the function of

* Not only do the different tissues vary among themselves in their capacity to respond to the presence of a hormone, but they may possibly vary in this respect from time to time as the result of either local or distant influences.

one organ with the physiologic activity of the entire organism. Many, but not all, of the hormones in this group produce structural as well as chemical changes. If we were to accept Cannon's view that the adrenal medulla secretes epinephrine (adrenalin) during periods of emergency, we should have an example of a hormone which is co-ordinating the function of anatomically unrelated structures for a common purpose, namely, defense.

Terms relating to diseases of the endocrine glands.

—Diseases of the endocrine glands are usually, but not always, accompanied by quantitative changes in the secretory activity of the diseased organ. In some instances there is evidence to suggest that qualitative abnormalities of secretion may occur. In such cases it is thought that the gland synthesizes an abnormal chemical molecule which has hormonal properties that may differ materially from those manifested by the normal hormone. Some of the clinical phenomena which occur in conjunction with tumors of the adrenal cortex can best be explained by such a hypothesis.

The self-explanatory terms *hypofunction* and *hyperfunction* are used to designate quantitative departures from normal secretory activity. The terms *dysfunction* and *malfunction* are often used so loosely that they cease to have exact meaning. Sometimes they imply the production of an abnormal hormonal molecule. Again the terms seem to refer to secretory activity that may be essentially normal in both quality and quantity, but which is poorly timed in relation to the needs of the body as a whole or to the activity of other members of the endocrine system. Very often these terms are used to cover a multitude of endocrine sins, in which case they are about synonymous with the expression frequently used by patients: "I must have something wrong with my glands." They should not be used as descriptive or diagnostic terms unless the precise meaning that is intended is specifically defined.

The term *imbalance* is of use in gynecologic endocrinology to designate abnormal quantitative and possibly qualitative relationships among the various hormones that are involved in the maintenance of the menstrual cycle. When this term is used to describe nongynecologic endocrinopathies, the implied meaning is not always clear.

Finally, not infrequently terms such as *endocrine dyscrasia* are applied to conditions (for example, simple obesity) that are characterized by certain stigmas that are somewhat suggestive of an underlying endocrine disorder. In many of these conditions it is impossible with present methods to demonstrate by means of quantitative measurements any abnormality of the endocrine system. When such problems are encountered there is little to be gained by the use of a diagnostic term which incriminates either the endocrine system or its individual members.

Lesions most commonly associated with abnormalities of secretory activity.—It is frequently stated that abnormal secretory activity of an endocrine gland cannot be estimated by its histologic appearance. This statement is only partially true, because in most instances bona fide endocrine disease is usually found to be attended by some histopathologic change in the particular organ at fault. The severity of the clinical symptoms, however, may not always be commensurate either with the gross or the microscopic pathologic findings. For example, the physician occasionally sees instances of severe exophthalmic goiter associated with comparatively slight alterations in the histologic appearance of the thyroid gland. In spite of such lack of correlation that may be obtained in certain diseases, in the main it may be stated that organic endocrine diseases are usually associated with structural changes in the gland at fault.

In this connection it should be recalled that the endocrine glands, even though they are anatomically normal, cannot function unless they are supplied with adequate raw materials (minerals, vitamins and other foodstuffs) from which hormones can be synthesized. Furthermore, the function of certain endocrine organs, notably the anterior lobe of the pituitary body and the gonads, is dependent to a considerable extent on the general health of the body.

Bearing in mind, then, the limitations of the conclusions that can be drawn from pathologic findings, one can summarize the lesions that are most commonly found in conjunction with abnormalities of secretory activity as follows:

1. *Glandular hyperfunction* is usually associated with (a)

diffuse hyperplasia* or hypertrophy of the entire gland, or with (b) adenomatous or malignant tumors. Such tumors often are functioning entities whose secretory activity is not under the control of those mechanisms which regulate the secretion of the normal gland. Hence, they continue to secrete without regard to the requirements of the body for their hormones.

2. *Primary glandular hypofunction* is frequently found in conjunction either with (a) hypoplastic lesions, or (b) destructive lesions of the glandular parenchyma, such as atrophy, fibrosis, destructive hemorrhage, acute inflammations, tuberculosis and other chronic inflammatory processes, granulomatous lesions, hemochromatosis, amyloid disease, metastatic malignancy and nonfunctioning or infiltrating neoplasms. Most of the glands have relatively large factors of safety, so that most of the parenchyma has to be destroyed before symptoms of hypofunction make their appearance. Furthermore, there is a great deal of evidence to suggest that as progressive lesions destroy more and more of the gland, the residual healthy glandular tissue compensates by becoming hypertrophic. This phenomenon can best be observed in the case of the paired ductless glands.

Secondary glandular hypofunction occurs as the result of anterior pituitary insufficiency. The latter may follow either as the result of an organic lesion of the pituitary body or as the result of metabolic disorders, poor hygienic conditions or systemic disease elsewhere in the body.

Relation of adenomatous tissue to endocrine function.—An understanding of the peculiar relationship of adeno-

* We have used the term "hyperplasia" somewhat loosely to designate the nonneoplastic parenchymatous enlargement of a ductless gland. Unquestionably in some instances the term "parenchymatous hypertrophy" would be preferable; in others, our knowledge of the histopathology is not sufficient to justify the selection of either term in preference to the other.

The word "adenoma" is a generic term that has been used to denote any benign epithelial tumor with a gland-like structure. It has been applied to a variety of lesions that exhibit such adenoma-like morphology. In addition the term often connotes a pathologic process which has a histologic resemblance to the architecture and a secretory resemblance to the physiology of the tissue from which the tumor arose. The rigid denotation of the word is gradually giving way, especially in endocrinologic literature, to its more useful connotation. In the ensuing series of papers the term should not be interpreted in its strict morphologic sense.

matous tissue to endocrine glandular function is so important that it is worth while to recapitulate:

1. Adenomas without clinical evidence of hyperfunction are frequently found at necropsy. This finding does not imply that such adenomas were not functioning. It usually does signify that the sum total of hormone that was made by the adenomatous and nonadenomatous tissue *was not excessive*.

2. The outstanding characteristic of hyperfunctioning adenomas is their tendency to function *irrespective of the needs of the body*. Apparently, they are not inhibited by the normal mechanisms that regulate glandular secretory activity.

3. When adenomatous tissue hyperfunctions, the remaining nonadenomatous glandular tissue from which the adenoma was derived tends to hypofunction and may become *functionally inadequate* or even *actually atrophic*. Such atrophic tissue usually regenerates if the adenoma is removed, but until regeneration or renewal of function does occur there may be a period in which the body suffers from an inadequate supply of the hormone that had been manufactured by the adenoma. The temporary diabetes that follows the removal of a hyperfunctioning tumor of the islets of Langerhans illustrates this point nicely. More important, however, are the cortical adrenal insufficiency and the tetany that occur after the removal of adrenal cortical tumors and tumors of the parathyroid bodies. The application of this principle to adenomas of the thyroid gland has not been demonstrated.

Fundamental principles of treatment.—The mechanism that determines the secretory activity of the endocrine organs is not known. It is frequently stated that the anterior lobe of the pituitary body is a "master gland" that "controls" the functional activity of the remaining members of the endocrine system. We do not feel that the available evidence at present justifies the unqualified acceptance of this conception of anterior pituitary function. The problems involved have more than academic significance, because there has been a tendency to look upon (and treat accordingly) the anterior pituitary body as the primary cause of a number of both endocrine and nonendocrine diseases of unknown etiology. On the whole, the therapeutic accomplishments that have sprung from this philosophy have been singularly unsuccessful.

The fundamental principles of the treatment of endocrine disorders are relatively simple. They may, however, be exceedingly difficult to apply. With few exceptions, the effective treatment of *hyperfunctioning* lesions is *surgical*. If the lesion is a benign or operable neoplasm, the surgical removal of the tumor usually results in cure. On the other hand, if the lesion is hyperplastic in character, the surgical reduction of the mass of hyperplastic tissue is less likely to be of benefit except in cases of exophthalmic goiter. If, for various reasons, surgical treatment is inadvisable (as is the case with certain types of pituitary tumor), roentgen therapy may reduce the mass of hyperfunctioning tissue.

Attempts to depress the *hormonal output* of hyperplastic or neoplastic tissue are frequently made by administering large amounts of a hormone that is thought to be directly or indirectly antagonistic to the gland that is diseased. The rationale behind this type of therapy at first sight appears highly logical. However, it does not take cognizance of the crucial fact that the lesions which are responsible for the symptoms are probably no longer amenable to control mechanisms. In addition to the weakness of the theory, there remains the very valid objection that, on the whole, this type of therapy has yielded either unsatisfactory or equivocal results. This statement is not vitiated by the fact that menopausal symptoms can be treated successfully by estrogenic substances. The menopause is not a "disease" and its attending symptoms are not the result of *hyperplastic* or *neoplastic* disturbances of the ovaries or the anterior pituitary body.

If an endocrine gland is destroyed or incapacitated by disease, the resulting symptoms of *hypofunction* usually can be controlled by the administration of its hormone. Such *replacement therapy* is limited necessarily by the availability of potent hormonal preparations and to some extent by the degree of similitude of the effects produced by the administration of the hormone to the normal action of the gland itself. For example, the treatment of severe diabetes mellitus is not always entirely satisfactory because of the differences between periodic injections of insulin and the secretion of insulin by the normal pancreas. In spite of its limitations, replacement therapy is of great value in many of the various endocrine insufficiencies.

Thus far, however, it has been of very little value in the treatment of severe degrees of anterior pituitary insufficiency such as the physician sees, for example, in instances of chromophobe pituitary tumor.

Replacement therapy should be sharply distinguished from *stimulating* therapy. The former is indicated when an endocrine gland is hopelessly damaged as the result of disease; the latter, when a gland is anatomically capable of functioning but for various reasons does not do so. The anterior lobe of the pituitary body and the ovaries seem to be particularly sensitive to extraneous influences which interfere with normal function, and it is in such conditions that stimulating therapy has the greatest usefulness. Hygienic regimens, vitamin and dietary therapy and "stimulating" doses of roentgen rays are among the measures in this category that are frequently used. When administered to experimental animals, the various extracts that have been prepared from the anterior lobe of the pituitary body seem to have specific stimulating properties on some of the other endocrine organs. With few exceptions comparable results have not been obtained in clinical medicine. The hormonal "pituitary-like" substances that are present in the blood and urine during pregnancy have been prepared for clinical use. These substances have the property of stimulating ovarian and testicular function. They have been shown to be of value in the treatment of certain gynecologic disorders (see Dr. Randall's article), and in the treatment of undescended testes and delayed puberty in boys.

Here again a word of caution is necessary because of the tendency to prescribe them in cases in which both the diagnosis and the necessity of treatment have been indeterminate. *Indiscriminate* endocrine therapy of this type not only may be physically injurious, but it is often the instigator of severe anxiety states. Furthermore, it is always expensive. If the use of any of these substances is contemplated, it is advisable to bear in mind the fact that hormones act on specific receptors and that the response to stimulation by anterior pituitary or anterior-pituitary-like hormones will be dependent on the capacity of the cells in the receptor to respond.

Replacement therapy should not be used indiscriminately. It does not stimulate either a normal or a diseased gland to

produce its own hormone, and as a general rule, therefore, it should not be administered when the objective in view is an increase in the ability of a gland to deliver its own product. In fact, long-continued administration of a hormone in large amounts may actually inhibit the secretory activity of any healthy tissue which is secreting that hormone, so that the end result is a situation comparable to disuse atrophy.

Fifteen years ago the subject of glandular therapy was discussed in a series of articles prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association. The introductory article was written by Dr. Frank Billings. After commenting on the difficulties in the "differentiation between the morbid conditions due to deficiencies of secretions of the internal glands and deficiencies in growth, development and other morbid conditions due to want of sunlight and a properly balanced diet" and on the lack of knowledge of the specific glandular principles that were "contained in the preparations used orally, subcutaneously, intravenously or as enemas," he concluded his discussion with the following remarks:

"It must therefore be admitted that, at present, substitutional organo-therapy in the treatment of conditions alleged to be due to deficiencies of the glands of internal secretion, with the exception of the thyroid and pancreas, cannot be utilized in general practice with the hope that definite results will be obtained. This should not, however, deter experimental substitutional organo-therapy by clinicians on animals and patients under conditions that will insure scientific accuracy. The experimental studies might well include the transplantation of glands including the gonads, with the hope that this type of organo-therapy may become of real benefit when rationally indicated and utilized.

"The brilliant results attending the use of preparations of the thyroid, including thyroxin, and of insulin afford reasonable belief that other important glands of internal secretion will be found to yield active principles that will arm us with specific agents for the correction of morbid conditions due to deficiencies of secretion of the respective glands. In the meantime, recognizing our responsibility to the public in this as in other matters that affect the welfare of the people, we should not continue to patronize and support those manufacturers of glandular remedies who make statements of specific virtues possessed by pluriglandular preparations that are without foundation of fact. The existence and continued pernicious influence of the manufacturers of glandular products who publish statements of their therapeutic value without the support of established physiologic and clinical facts will depend on whether the medical profession will patronize them. A decided forward step would

be taken if physicians were to limit their use of animal organ preparations to those admitted to the United States Pharmacopoeia and the current edition of New and Nonofficial Remedies.

"The endeavor has been made to present in this introductory statement the present status of organotherapy as based on existing knowledge of the physiology, both normal and pathologic, of the glands of internal secretion. The judgment and the conclusions formed in regard to problems in biology that are not fully understood today may require a change of opinion and verdict in the future. Therefore, the opinions and judgment expressed in this brief statement in regard to the value of organotherapy today may require readjustment tomorrow."

That remarkable progress has been made in the intervening years is immediately apparent, and that the fundamental philosophy of Dr. Billings regarding endocrine therapy is as sound today as it was the day on which it was written needs no comment.

DISEASES OF THE PITUITARY GLAND

EDWARD H. RYNENARSON AND EDWIN J. KEPLER

Introduction.—A number of articles in this symposium on the endocrine glands have been designed to emphasize the treatment of the various abnormalities which arise from overfunction and underfunction of these glands. For the pituitary gland, however, this is not only difficult but virtually impossible. This difficulty is due first of all to the fact that our fundamental knowledge regarding the functions of the pituitary gland is of such recent date and, second, to the fact that clinicians have not been supplied as yet with extracts prepared from the anterior lobe of the pituitary gland which are effective when used for man. These remarks do not apply to the *posterior* lobe of the pituitary, regarding which our knowledge is much more mature and for which we have at our disposal hormones which are effective and which have been given adequate therapeutic trial.

This paper will, therefore, be concerned more largely with recapitulation of some of the knowledge which we have regarding the pituitary gland. It is, of course, impossible to go into any great detail, and those who are interested in doing this are referred to such volumes as "The Pituitary Gland: An Investigation of the Most Recent Advances," and "The Physiology and Pharmacology of the Pituitary Body." "Endocrinology," the Bulletin of The Association for the Study of Internal Secretions, contains reviews. One review was published in 1938 in the "Archives of Internal Medicine"; a subsequent review is being prepared at present for publication in the same journal. A chapter on "Diseases of the Ductless Glands," written by one of us (Kepler) and Boland for a book by Yater, has been consulted freely in preparation of this article.

Anatomy.—A discussion of gross anatomic relations of the pituitary body that are of clinical significance in connection with intrasellar expanding lesions will be found in the paper on

chromophobe tumors by Dr. Sheldon. Our discussion, therefore, has been limited to a brief presentation of certain embryologic features and to some of the newer work which has been done on the nerve supply, blood supply and neural connections of this organ. In this connection the work of Tilney, Rasmussen, Wislocki, and Aura E. Severinghaus is of particular value.

Morphologically and physiologically, the pituitary body should be regarded as at least two distinct units, namely, the *anterior lobe* (pars distalis, adenohypophysis) and the *posterior lobe* (pars nervosa, processus infundibuli). It is generally believed that both the anterior and posterior lobes are of ectodermal origin. The anterior lobe arises from somatic ectoderm in the region of the mouth (Rathke's pouch). Ultimately the anterior lobe becomes detached from the roof of the mouth by the obliteration of its duct, although the "craniopharyngeal canal" in the sphenoid bone sometimes marks the site of the primitive duct. As the epithelium grows upward it encounters a knob-like expansion of the infundibulum (the posterior lobe) that has arisen from the neural ectoderm in the floor of the third ventricle. As development progresses, the posterior lobe rests snugly in a concavity of the anterior lobe and, according to Cushing, resembles "a ball that is held in a catcher's mitt."

There is still some uncertainty regarding the exact manner by which the pituitary body of man is supplied with blood. The most recent studies indicate that the anterior lobe and stalk are supplied by the several superior hypophysial arteries that arise from the internal carotid and posterior communicating arteries, and that the free end of the posterior lobe is supplied by the inferior hypophysial arteries, which in turn take their origin from the internal carotid arteries in the cavernous sinuses. The venous blood leaves the pituitary body by way of venules that drain directly into the adjacent cavernous or intercavernous sinuses. In addition there is a system of portal veins that connect the capillary plexus of the stalk with the arterial sinusoids of the anterior lobe. There is thus abundant opportunity for collateral circulation through the capillary-sinusoidal bed of the posterior and anterior lobes.

Rasmussen has shown that the anterior lobe, in sharp contrast to the posterior lobe, is devoid of any direct neural con-

nections with the nuclei in the floor of the third ventricle. The comparatively few fibers that are found in the anterior lobe are derived from the cavernous sympathetic plexus and are probably vasomotor fibers. The posterior lobe, on the other hand, is unquestionably connected by way of tracts that pass down the stalk with the nuclei of the floor of the third ventricle. Chief among these tracts is the tractus supra-opticohypophys-eus, which originates in the supra-optic nuclei. According to Rasmussen, although there are at least 100,000 fibers which descend through the stalk into the infundibular process, yet there is no worth-while evidence that more than a negligible number of nerve fibers from this source enter into the anterior lobe of the pituitary body of the human being.

On anatomic grounds, therefore, a neurohumoral pathway exists by which neural impulses to the posterior lobe conceivably might set up secretory activity of part of the anterior lobe. However, conclusive evidence has never been presented to show that hormonal discharge from the anterior pituitary body may result from neural stimuli. The well-known fact that ovulation of the rabbit does not occur until after coitus, however, is suggestive that function of anterior lobe might be incited by impulses traversing neural pathways.

Cytology.—This subject has been discussed completely by Severinghaus. He listed the known types of cells in the anterior lobe of the pituitary. The three which are normally present are the *acidophil* (sometimes referred to as the "eosinophil"), whose cytoplasmic granules stain brilliantly with acid or plasma dyes; the *basophil*, whose cytoplasmic granules are less distinct and more irregular in size and form than those of the acidophil and take the basic dyes; and the *chromophobe*, whose cytoplasm is devoid of specific granulation. In addition to these three types of cells, two others have been associated with special conditions: (1) the "*signet ring*" or *castration cell*, which is found in the anterior lobes of castrated animals of certain species and is a modified basophil, and (2) the "*pregnancy cell*," found during and after pregnancy, which was originally described in the human as a modified acidophilic type.

After reviewing the evidence available from clinical and experimental sources Severinghaus summarized his views on

the cytologic changes that accompany physiologic and pathologic processes as follows:

"Growth phenomena as seen in acromegaly and in the dwarf mice are unquestionably related to the acidophile cells. In pregnancy both the acidophiles and basophiles actively secrete. They are then jointly concerned with the reproductive phenomena involved in the pregnant state. Castration, likewise, has its effect on both cell types, although the increase of basophiles seems the more prominent alteration. This increase is associated with greater gonad-stimulating potency, and has, therefore, linked the basophile to the production of the hormone involved. It is almost certain, however, that two gonad-stimulating hormones are elaborated, and there is evidence to indicate that the acidophile may also be a source of one of these. Injections of pregnancy urine and of gonadal hormones, likewise, have their effect on both granular types of cells, although males and females do not respond similarly to all injections. This is additional evidence that both cells take part in the hypophyseal control of gonad activity. Thyroidectomy and thyroid administration, likewise, affect both granular cells, and in some respects these effects are not unlike those produced by disturbances in the gonadal relationship. This not only indicates that we may not yet eliminate either cell type from thyroid relationship but it emphasizes the necessity of further study of thyroid-gonadal relationships and their joint reactions with the anterior hypophysis. One should like to give way to over optimism or enthusiasm and say that with the rapid advances of experimental and cytological researches during the last few years, the time will not be far distant when we can speak with certainty of the hormones of the anterior lobe and the cells responsible for their elaboration. When that day comes, the cytologist, at least, expects that the number of anterior lobe hormones will be much fewer than it is today, and that the varying responses of the organism will be interpreted as individual reactions to a given hormone rather than responses to individual hormones."

As one might expect, these concepts of Severinghaus have not been universally accepted. From a purely clinical point of view one is tempted to attribute the origin of the growth-promoting substance to the acidophilic cells, the gonadotropic

principles to the basophilic cells, and the various principles that influence specific metabolic processes to either one or both types of cells. Evidence from all sources indicates that the chromophobe cell is without secretory function.

Physiology.—Knowledge regarding the physiology of the anterior lobe has been gained in several ways. The first experimental observations were made by studying animals after the surgical removal of the pituitary. It was found that there is abrupt and permanent cessation of growth. This cessation of growth refers largely to skeletal growth, for incisions do heal, hair does cover the scar and, if one kidney is removed, the other hypertrophies. How much of this lack of body growth is due to the animal's loss of appetite has not been determined satisfactorily. The viscera, particularly the endocrine glands, markedly regress. As a result of this secondary atrophy of the endocrine glands, other changes are observed, such as decrease in the basal metabolic rate, cessation of all sexual functions and lactation, hypoglycemia, marked sensitivity to insulin, both medullar and cortical adrenal insufficiency and so forth. The transplantation of pituitary glands or the injection of suitably prepared pituitary extracts into normal and hypophysectomized animals has also been of value in studying pituitary physiology. For example, it has been found possible in hypophysectomized animals adequately to restore the animal's functions by these methods, and in normal animals to produce effects comparable to those that occur in certain diseases of the pituitary body.

Of the several obvious objections to these studies on experimental animals, only three will be mentioned: 1. It is virtually impossible to operate on the pituitary gland of any animal without producing an effect on contiguous structures. We are aware of the control experiments, including sham operations, but we doubt if these invalidate this primary criticism. 2. It is unwise to assume that any effect noted after the injection of a pituitary extract is necessarily a specific effect. The changes that occur may be due to secondary action from the interaction of one, two, or more associated endocrine glands, or even to a nonspecific response of the body as a whole. 3. There is a marked difference among species of animals, so that results of a certain experiment may be definite and clear-cut with one

type of laboratory animal but may be contradictory or inconclusive in another species. This fact has contributed greatly to the confusion in attempting to evaluate published reports of experimental studies.

The second method by which the physiology of the pituitary gland has been studied is largely based upon careful observation of patients suffering from various disturbances of the endocrine glands. This type of knowledge long preceded any experimental studies and our first knowledge of the function of the pituitary came from clinicians who observed the changes in cases of acromegaly, dwarfism, chromophobe adenomas and so forth. Two difficulties in evaluating observations regarding the physiology of the pituitary from the study of patients will be mentioned. The first is the confusion which results from the differing diagnoses of pathologic states. For example, the condition of one patient may be diagnosed as Fröhlich's syndrome by one physician, but another physician, seeing the same patient, will give an opinion that the boy, although fat and underdeveloped sexually, does not have true Fröhlich's syndrome. The second difficulty is that clinicians have not had available for use sufficient quantities of satisfactory potent extracts of the pituitary in order to study their effect on human beings.

We have no idea how many hormones are secreted by the anterior lobe of the pituitary. We would be far safer if we were to speak of principles having differing effects rather than of different hormones, for it is improbable that one gland composed of only two known types of secreting cells can produce all of the separate hormones which are credited to it. Specific fractions having hormonal properties have been prepared from extracts of the anterior lobe.

1. *The growth principle.*—There is considerable controversy as to whether there is a specific growth hormone, and this controversy, which is being conducted largely by Evans and Riddle, has been discussed in detail in their respective articles. Certain it is that Evans has been able to induce the growth of hypophysectomized animals with extracts which he stated are free from effect on other glands. With this statement Riddle is in disagreement and, for the present, no conclusion can be drawn.

2. *Thyrotropic principle*.—This fraction restores to normal the cells of the thyroid gland which have atrophied as a result of hypophysectomy, or it will cause hyperplasia of normally flattened epithelium in certain animals, such as the guinea-pig. When injected into human beings or animals, it causes an increase in the basal metabolic rate, if a thyroid gland that is capable of functioning is present.

3. *The gonadotropic principle*.—At present there are believed to be two of these substances: (1) *follicle-stimulating*, which stimulates the follicles in the ovary and the germinal epithelium in the male, and (2) *lutinizing*, which stimulates the development of the lutein cells in the ovary and the interstitial cells and accessory sex glands of the male. Other gonadotropic fractions have been described but have not been accepted generally. As a matter of fact, some authors have stated that there is only one gonadotropic hormone which has different quantitative effects.

4. *The adrenocorticotropic principle*.—This substance repairs the atrophy that occurs in the adrenal glands of hypophysectomized animals.

5. *The mammotropic or lactogenic principle*.—When this is injected into animals, it causes development and lactation of the breasts. This is the only hormone which has been isolated in crystalline form.

6. *The diabetogenic principle*.—This substance has a distinct effect on carbohydrate metabolism. Young, of England; Campbell and Best, of Toronto; and Dohan and Lukens, of this country, have been able to produce permanent diabetes mellitus in dogs by the use of this substance. There can be no doubt regarding the fact that the anterior lobe of the pituitary gland does have an effect on carbohydrate metabolism. This fact was first proved by observations made on the "Houssay dog." Houssay first showed that the diabetes of a dog following pancreatectomy can be alleviated by subsequent hypophysectomy. It is interesting to note that Long produced virtually identical results by adrenalectomy rather than hypophysectomy.

7. *A ketogenic principle*.—This substance induces the development of ketone bodies. The existence of such a hormone is in considerable doubt.

8. A *parathyrotropic principle*.—Its existence also is in doubt.

9. Separate principles have been described having effects on the *metabolism of carbohydrate, protein, fat, and water*.

10. A *specific metabolic principle* had been described.

11. A *hematopoietic "hormone"* has been suggested.

In addition to the effects produced by these substances, many other effects have been reported. From this very brief discussion it must be obvious that a tremendous amount of work must be done in the future before our knowledge regarding the number and character of the true hormones of the anterior pituitary is complete. Until laboratory scientists with thousands of animals at their disposal tell us how many hormones there really are, describe their known effects, and prepare them in pure form and in sufficient quantity for human injection, how can a clinician be expected to evaluate their effectiveness for human use? It is also a fact that with very few exceptions the effects listed have not been *consistently* obtained when these various substances have been given to the human being, a statement which is both discouraging and true.

Pathology.—The usual pathologic processes which can involve any other glands of internal secretion are also found in the pituitary gland. These have been listed by Rasmussen as (1) *destructive lesions*, (2) *adenomas*, (3) *other tumors*, (4) *animal parasites*, and (5) *craniopharyngiomas* and *suprasellar cysts* which, by their location, cause a destruction of the pituitary and secondary interference with function of the gland. These tumors may invade the sella turcica, may more or less destroy the hypophysis, and may grow into the third ventricle as other large tumors in this region do.

The two types of pathologic processes which deserve special mention are the first two. If *destructive lesions* occur in early life, *dwarfism* or *infantilism* in one form or another usually results. Extensive necrosis or atrophy of the anterior lobe in later life may be followed by *hypophysial cachexia* or *Simmonds' disease*. The clinical aspects of this will be taken up later. The most common destructive agents are puerperal sepsis, emboli, thrombi, tumors, cysts, tuberculosis and syphilis. The effects of lesions in the pars tuberalis are complicated by the possibility of injury to adjacent brain structures, and such

injury is frequently followed by adiposogenital dystrophy or Fröblich's syndrome.

The second major type of pathologic process is the *adenoma* of the anterior lobe. In a recent series of 1000 routine necropsies performed at The Mayo Clinic on subjects who were not suspected during life of having hypophysial involvement, Costello found adenomas in 22 per cent.* Most of these adenomas were only a fraction of a millimeter to a few millimeters in size, but some were more than 1 cm. in size and had gone unrecognized while the patient was alive. Thus, it can be seen that it is possible to have an adenoma of the pituitary which does not produce any recognizable effect. Rasmussen pointed out that "according to the kind of cells involved, hypophysial adenomas are of four types: Chromophobic, acidophilic, basophilic, and mixed. They are seldom multiple. Chromophobe adenomas are by far the most prevalent and may become several centimeters in diameter. *Basophil adenomas* are the least frequent and are small, frequently being microscopic, making it difficult to evaluate statistics on their incidence, because there is no sharp line of demarcation between them and extra large groups of ordinary (normal) basophils.

"*Chromophobe adenomas* give rise to symptoms largely because of pressure, displacement, or actual destruction of the rest of the hypophysis, and because of encroachment upon neighboring brain structures such as the optic chiasm and tuber cinereum.

"*Acidophil adenomas* of sufficient size usually cause hyperpituitarism. The alpha cells are apparently liberating a growth hormone. If preadolescent, there is delayed union of the epiphyses and gigantism may result. Most of the large giants show evidence of pituitary pathology. If postadolescent, there follows a symptom-complex known as acromegaly (overgrowth of connective tissue, including bone, with the resulting enlargement of hands, feet, jaw, lip, and so forth). The prominence of the symptoms is more or less proportional to the intensity of the acidophilia of the neoplasm. In progressive cases, the

* Compare: Ecker, A. D.: The hyaline change in the basophil cells of the pituitary gland not associated with basophilism. *Endocrinology*, 23: 609-617 (Nov.) 1938. Also: Anatomic associations of pituitary basophilism. *Proc. Staff Meet., Mayo Clin.*, 14: 200-202 (Mar. 29) 1939.

tumor may become large enough to cause neighborhood signs, such as bitemporal hemianopsia.

"*Basophil adenomas*, once considered almost nonexistent, have recently received much attention as an etiological factor in the pluriglandular syndrome (sudden adiposity, striae atrophicae, hirsuties, sexual abnormalities, elevated blood pressure, glycosuria or lowered sugar tolerance, osteoporosis, dusky or florid face, and bruising easily) which Cushing,^{12, 13} in 1932, called *pituitary basophilism*, but designated *adipositas osteoporotica endocrinica* by Askanazy and *hypophysial plethora* by Jamin. It is now realized that this syndrome occurs without any basophil tumor or demonstrable basophilic hypertrophy or hyperplasia in the hypophysis. Most of the patients have hypertrophy of the adrenal cortex. Since the electrolytic pattern of the plasma tends to be diametrically opposed to that in Addison's disease, which is clearly hypocorticoadrenalism; McQuarrie²⁴ suggests *hypercorticoadrenalism* for the syndrome. A large percentage has adrenal cortical tumors. Some (e.g., Goldzieher and Koster) attempt to differentiate between the pituitary cases and those due to adrenal cortical tumors. Kessel presents a summary and the literature.

"A few cases have no adenoma of the hypophysis and no obvious pathology in the suprarenals. . . .

"The pathology that has been found to be most constant in pituitary basophilism is a hyaline change in the cytoplasm of at least some of the basophils of the anterior lobe, as first described by Crooke."

SYNDROMES ASSOCIATED WITH HYPOFUNCTION OF THE ANTERIOR PITUITARY

Dwarfism and infantilism.—It is extremely difficult to define "dwarfism." Is every undersized individual a dwarf? The confusion which exists is well illustrated by the attempt to classify dwarfs and to define the pathologic characteristics of each group. There are those dwarfs who are described as "disproportionate" and whose deformity is not known to be related to the pituitary gland. Examples are the rachitic, the achondroplastic and the cretinoid dwarfs. The proportionate dwarfs are those whose bodies are neither deformed nor distorted. There are at least two types of these. The first is the

"primordial" dwarf whose size is an hereditary trait. They are normally developed in every way and, with normal sexual power, reproduce their own unfortunate species. The second type of proportionate dwarf is the infantile dwarf (Fig. 120) who, born to normal parents, fails to grow normally and never undergoes sexual maturity and never develops associated sexual

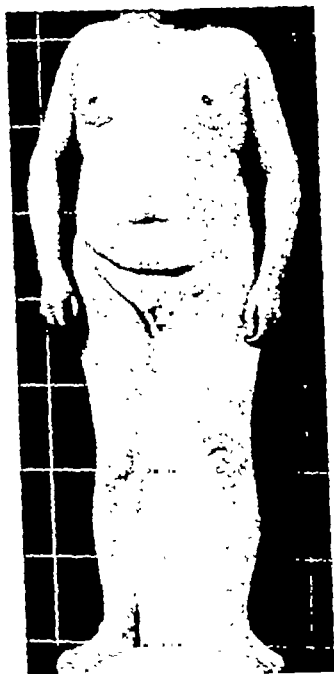


Fig. 120.—Dwarfism.

characteristics. In 1908, Ettore Levi, of Florence, correlated Lorain's type (previously ascribed to malnutrition and hereditary influences) with pituitary disease. The term "Lorain-Levi's infantilism or dwarfism" has been applied to this condition. These individuals probably have this condition as the result of disturbances of the anterior lobe of the pituitary.

[N. B.: Figs. 120, 121, and 124 previously appeared in Kepler, E. J. and Boland, E. W.: *Diseases of the Endocrine Glands*. In Yater, W. M.: *The Fundamentals of Internal Medicine*. New York, D. Appleton-Century Company, Inc., 1938, pp. 451-509.]

Barker has found four cases of dwarfism in which necropsy disclosed destruction of the pituitary from craniopharyngiomas.

Patients suffering from infantile dwarfism have been treated with all of the means at our disposal. Theoretically, the *growth hormone of the anterior pituitary* should restore them to normal size. Actually, we have found no such case in the medical literature in which the evidence presented could be considered as conclusive. The best study of this type of treatment was reported by Shelton, Cavanaugh and Evans, but neither they nor anyone else has reported complete restoration to normal size.

It is difficult to know how to classify *progeria*, a very rare condition in which, in addition to dwarfism, the individual looks



Fig. 121.—Fröhlich's syndrome.

prematurely old. The tiny, young individual has an old man's skin but in many respects, such as genital infantilism, never grows up.

The *Laurence-Moon-Biedl syndrome* is characterized by adiposogenital dystrophy, atypical retinitis pigmentosa, mental deficiency, familial occurrence and skeletal abnormalities, most frequently polydactylism and syndactylism. It has been described in detail by Reilly and Lissner. Insufficient evidence exists to determine the pathology of this syndrome.

Fröhlich's name has been given to the syndrome of dystrophia adiposogenitalis (Fig. 121) which he described in 1901. For the sake of accuracy, it should be noted that Babin-ski had reported the case of a similar patient in 1900, whom he had observed for ten years. A male patient with this syndrome

is unnaturally obese; the deposits of fat resemble those of the female, and produce large hips, breasts and mons veneris. The genital organs, both internal and external, remain underdeveloped; the testes may remain undescended. Secondary sexual characteristics do not develop. In the female, obesity is marked and amenorrhea is the rule. In neither sex is there sexual feeling or activity. In both sexes the skin is soft, pale, fine and hairless except for the scalp, where the hair is fine and silky. The epiphyses sometimes remain ununited and other skeletal changes are noted, as illustrated by the hands, which are small, and fat and have tapering fingers.

Too many patients are being given the diagnosis of *Frölich's syndrome*. The facts of the case are that it is really a rather rare condition, and every fat boy with delayed development does not have a craniopharyngioma which is destroying his pituitary. If let alone, most of these fat boys "straighten out" themselves and many of the "cures" reported following the use of endocrine preparations probably would have occurred if no treatment had been given. We have seen many instances in which treatment was delayed for six months or a year and complete restoration to normalcy occurred. If treatment had been used during this period, another report of cure might have been published. Operation on the pituitary should be advised only when *definite evidence of a tumor* exists and usually then only when the *visual fields* are being affected.

Simmonds' disease.—There is no doubt as to the entity of Simmonds' disease; there is room for considerable doubt as to its frequency. After a cursory perusal of the literature a physician would be inclined to believe that the disease is of rather frequent occurrence, that the diagnosis is clear, and that glandular treatment may be successful. What are the facts?

In 1914, Simmonds reported the findings in several cases in which a destructive lesion of the anterior hypophysis was demonstrated at necropsy. In his cases, and in the proved cases since reported, the following symptoms were almost always present: marked, rapid loss of weight, amenorrhea (the disease is predominantly found in women), loss of pubic and axillary hair, dry skin, low basal metabolic rate, hypoglycemia or a flat sugar tolerance curve, asthenia, psychic changes, hypotension, loss of libido and potentia. If, as some physicians

seem to believe, every patient with these symptoms has Simmonds' disease, then it is common indeed. But every one of these symptoms can be present in *anorexia nervosa*. One case of this syndrome was studied carefully at necropsy²⁵ and a perfectly normal pituitary was found.

How many proved cases of Simmonds' disease are there? Lissner and Escamilla have searched the world literature and have found only sixty-nine. Richardson, in a very searching

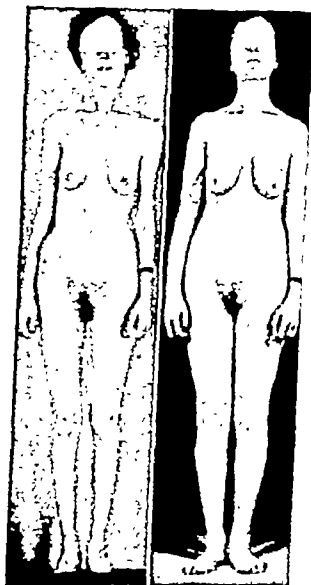


Fig. 122.—Anorexia nervosa. (From Richardson, H. B.: Simmonds' disease and anorexia nervosa. *Arch. Int. Med.*, 63: 1-28 [Jan.] 1939.)

article, pointed out the great difficulty in making this diagnosis. He stated: "In spite of all this the diagnosis during life remains completely uncertain. The reason is that most, if not all, the symptoms which are listed as characteristic of Simmonds' disease can be produced by simple inanition. This statement is based on studies reported in the literature and on the study of patients to be reported on here. The emaciation, appearance of age, gonadal atrophy, dental caries, splanchnomicria and depression of the basal metabolism may all be interpreted

as the result of starvation." He then described instances in which the diagnosis of Simmonds' disease was erroneously made and improvement was credited to endocrine therapy of one type or another. "The therapeutic test as reported in the literature is unreliable for one or more of the reasons given; namely, (1) too many remedies were used simultaneously, (2) the factor of suggestion was not controlled, (3) the improvement was not parallel with the use of medication, (4) the improvement persisted or even increased when the medication was discontinued and (5) the usual dose was altogether inadequate."

Evidence of the rapid and complete return to health of a patient with anorexia nervosa who was treated only with reassurance, a high calorie diet and vitamin supplements is recorded in Fig. 122. The picture should be memorized by those who base the diagnosis of Simmonds' disease on the response of the patient to the injection of hormones!

We wish to emphasize (1) that Simmonds' disease is an entity, (2) that it is extremely rare, (3) that many of the patients reported to be suffering from Simmonds' disease really have anorexia nervosa and (4) that therapeutic response is a poor basis for diagnosis.

Hypopituitarism associated with chromophobe adenomas of the anterior lobe.—So far as is known, the chromophobe cells do not secrete any hormones. Chromophobe tumors are the most common of all pituitary tumors, and they produce symptoms because of their location. The endocrine symptoms probably occur because of pressure on the secreting eosinophilic and basophilic cells. As long as they are small, the symptoms are minimal or absent. Ultimately, however, they escape the confines of the sella turcica and encroach on the suprasellar structures. When this occurs visual symptoms and other symptoms referable to the vegetative diencephalic structures result. Only the endocrine symptoms will be considered at this time. A detailed discussion of the other symptoms will be found in the paper by Dr. Shelden.

Amenorrhea, or its masculine analogue, impotence, is often the initial symptom and may remain the only endocrine symptom. The amenorrhea is not associated with hot flushes or

other menopausal symptoms. When the endocrine symptoms become more marked, the skin becomes thin and smooth and assumes a characteristic waxy pallor. A loss of cutaneous hair occurs, especially noticeable in the sparse, slow-growing beard of the male. Weakness, intolerance to cold, and obesity occur; obesity in the male assumes the characteristics of obesity in the female. Diabetes insipidus occurs only infrequently and, when it does, it rarely is permanent. The basal metabolic rate is low, there may be slight or marked initial hypoglycemia, and the glucose tolerance curve is often flattened. Hypoglycemia sometimes occurs but hypoglycemic symptoms are rare. Pituitary (Simmonds) cachexia has been observed in isolated instances.

If the patient presents himself because of *intracranial symptoms*, such as headache or impairment of vision, the diagnosis usually is not difficult. On the other hand, if the patient's complaints are the result of *mild hypopituitarism*, the diagnosis may be difficult to make, especially if headache or visual disturbances are not present. In such cases the peculiar and distinctive waxy pallor, taken in conjunction with the sparse beard and sparse genital and axillary hair, will give a clue. The disease may be more difficult to recognize in men than in women, because men may not mention impotence as a symptom whereas women usually lay stress on amenorrhea. Because of such symptoms as pallor, weakness, intolerance to cold, and so forth, myxedema and pernicious anemia most often are suggested in the differential diagnosis. Patients suffering from myxedema have coarse dry skin and do not lose their pubic and axillary hair, or, in the case of men, their beards. Defects in the perimetric fields or an enlarged, eroded sella turcica, or both, are valuable aids in making the diagnosis of chromophobe adenoma.

Surgical intervention usually is indicated when vision is impaired. *Roentgen therapy* has given good results in a fair proportion of cases. *Replacement therapy* eventually may prove to be of value in the treatment of the endocrine symptoms which persist after operation or occur in inoperable cases. At present, endocrine therapy is far from satisfactory in these cases.

DISORDERS ASSOCIATED WITH HYPERFUNCTION OF THE ANTERIOR LOBE

As has been mentioned under cytology, only two types of cells in the pituitary are known to secrete hormones: the eosinophil and the basophil. It is theoretically possible for these cells to secrete an excessive amount of hormone without the development of an actual tumor, and this may explain to some extent why confusing clinical pictures can arise which cannot be attributed to tumor formation; however, in far the greatest percentage of cases of this type definite evidence of a tumor of one type of cell or the other exists. If such a tumor attains sufficient size to compress and destroy the nontumorous pituitary parenchyma, a confusing clinical picture results which is characterized in part by the signs of hypopituitarism, and in part by the signs that result from the hypersecreting tumor. It should also be remembered that any expanding lesion of the anterior lobe of the pituitary may produce disturbances of function in the posterior lobe or the important nerve centers in the diencephalon.

Gigantism and acromegaly.—There is no evidence to indicate that these conditions are essentially different. Both are caused by the excessive production of the growth hormone from a tumor or hyperplasia of the eosinophilic cells. If this condition develops before the ossification centers are complete, then *gigantism* (Fig. 123) is produced, the most notable case being "the Alton giant," who at the time of writing is still alive and still growing. If the excessive output of the hormone occurs after closure of the epiphyses is complete, the resultant deformity is called *acromegaly*. This condition is characterized by overgrowth of the short and long bones, by enlargement of the viscera, changes in the muscles and by hypertrophy of the skin and connective tissues. For some time the term "*cutis verticis gyrata*" existed in the literature. The skin of the scalp was so hypertrophied as to produce long furrows. This is now acknowledged to be simply one of the symptoms of *acromegaly*.

The early *symptoms of acromegaly* are variable: An increase in general strength, in libido and potentia, or in mental capacity are not uncommon initial observations. The face, hands and feet slowly grow larger. The supra-orbital ridges

become prominent, and the mandible enlarges and protrudes (prognathism). The teeth become separated and the malar and zygomatic arches are prominent. The skull enlarges, the face lengthens, and the connective tissues thicken. The lips become large and the tongue may be enormous. The hands are big and broad with thick, blunted fingers, producing the so-called spade hand. The feet are correspondingly large.



Fig. 123.—Gigantism and dwarfism. (Falta, W.: *Die Erkrankungen der Blutdrüsen.*)

Hypertrophy of all of the visceral organs, especially the heart, is the rule. Changes in the vertebrae may be noted, and the development of kyphosis is not uncommon. As the disease progresses, great loss of strength ensues. Amenorrhea or impotence usually occurs at some time during the course of the disease. A large tumor may produce neurologic manifestations by compressing the surrounding structures. Intense headache is common. Impairment of vision, caused by encroachment of the tumor on the optic chiasm with the production of bi-

temporal hemianopia, is not uncommon. Choked disks rarely are produced. Roentgenologic examination usually reveals enlargement of the sella turcica and tufting of the ends of the terminal phalanges.

Hyperthyroidism and *acromegaly* frequently are associated. In such cases the thyroid is generally grossly or microscopically abnormal, usually as the result of adenomatous formation. In some of these instances the symptoms of hyperthyroidism are of sufficient severity to necessitate subtotal thyroidectomy, in spite of the high risk which this procedure entails. Whether or not the basal metabolic rate is elevated in acromegaly unassociated with organic changes in the thyroid gland is a matter about which opinion differs considerably. Frank or latent diabetes mellitus not infrequently accompanies acromegaly; in some instances the diabetes may be extremely severe and difficult to control. Hypertension is a relatively common finding among acromegalics.

Atkinson, in 1936¹ and 1938², reviewed the world literature concerning this subject. Certain phases of acromegaly have been studied separately. Courville and Mason studied twenty-four cases, from the standpoint of the heart particularly. They found that heart failure caused death in eighteen.

Both acromegaly and gigantism may burn out spontaneously, possibly as the result of cystic degeneration of the tumor. Even patients with progressive disease may go on satisfactorily for many years. Death may be produced by intercurrent infection, by the final cachexia of the disease, by congestive heart failure with or without hyperthyroidism, or by the pressure effect of a large tumor. Formerly, diabetic coma accounted for a fair percentage of the deaths.

The *treatment* of gigantism or acromegaly is unsatisfactory. Surgical removal of the responsible tumor is advised only when detailed examination of the visual fields gives evidence that blindness is likely to ensue. Numerous reports regarding roentgen treatment have been published, some of which give an account of careful studies and encouraging results. Because of the antagonism between ovarian and testicular hormones and the anterior lobe of the pituitary, treatment with estrogens and androgens has been suggested and given a brief but unconvincing trial.

Pituitary basophilism.—The clinical syndrome known as “pituitary basophilism,” or “Cushing’s syndrome” (Fig. 124), may be associated with a hyperfunctioning adenoma composed of basophilic cells. Similar, and at times identical, syndromes have been found to be associated with tumors or hyperplastic lesions of the adrenal cortex, thymic tumor, and arrhenoblastoma of the ovaries. When the syndrome results from baso-



Fig. 124.—Pituitary basophilism.

philic adenoma, it is often termed “Cushing’s disease.” In a few instances no significant or gross pathologic changes have been encountered at necropsy and the pituitary gland has been free from adenoma. The syndrome, therefore, is not a specific one limited to basophilic adenoma of the pituitary. The pathologic physiology of the disease is exceedingly obscure. The physiologic behavior of the gonads is not what might be expected from overproduction of gonadotropic hormone. On the

other hand, many of the symptoms and the high incidence of bilateral adrenal cortical hyperplasia in basophilism suggest that overproduction of adrenotropic hormone occurs. In spite of the fact that it is difficult to correlate what is known regarding the normal physiology of the anterior lobe of the pituitary with the symptoms of Cushing's disease, it is nevertheless convenient to consider it as being the result of basophilic hyperfunction.

Bona fide cases of Cushing's disease are exceedingly rare, the incidence probably being less than that of acromegaly. Young women are the chief victims, although the disease occurs among men.

Basophilic adenomas are benign, may be single or multiple, are usually small, and rarely produce enlargement of the sella turcica or neurologic manifestations. Because the tumors are small they may be overlooked at necropsy unless the pituitary gland is examined by serial sections. Basophilic adenomas are occasionally found at necropsy in cases in which there were no symptoms of basophilism.

The *symptoms* are predominantly endocrine and, in proved cases, the syndrome seems to be as constant in its manifestations as acromegaly. In women the initial symptoms are usually amenorrhea, hirsutism of the male type, and a peculiar type of obesity which is localized in the face, neck, and trunk, the extremities being comparatively thin. Simultaneously, the face becomes round and florid, so that the entire physiognomy is altered. Patients often state that their friends no longer recognize them. The hirsutism usually tends to increase and shaving often becomes necessary. As the disease progresses, the shoulders become rounded and the stature may shorten as the result of osteoporosis and collapse of the vertebrae. Purpuric spots and ecchymoses may appear on the extremities, and the skin of the abdomen, thighs, back, and sometimes the arms, becomes marked with broad, purplish atrophic striations. In addition to these changes in appearance, fatigue, and ultimately profound weakness, are the outstanding complaints. A variety of other symptoms, such as backache, abdominal pain, visual disturbances, pain in the eyes, choking, and sensations of suffocation, may be present. Convulsions and fainting spells occur occasionally.

The blood pressure is almost invariably elevated, ranging from 150 to 250 mm. of mercury systolic and from 100 to 155 mm. diastolic. Diabetes mellitus, either frank or latent, may be present. Roentgenographic evidence of osteoporosis is common, but the osteoporosis is not associated with the same type of chemical changes in the blood as that associated with hyperparathyroidism. When the disease affects males, the same cardinal symptoms occur, with the exception that amenorrhea is replaced by impotence. The disease is slowly progressive and generally terminates fatally.

The *diagnosis* of Cushing's disease is always fraught with uncertainties, and it should never be made until the other diseases which may be associated with Cushing's syndrome have been excluded. In doubtful cases the adrenal glands and pelvic organs should be explored surgically and efforts made to exclude thymic neoplasms.

Treatment is not very satisfactory. Roentgen therapy has been used with considerable success in isolated instances.

DISORDERS ASSOCIATED WITH HYPOFUNCTION OF THE POSTERIOR LOBE

Functions of the posterior lobe.—Although the function of the posterior lobe is not known definitely, experimental and clinical evidence suggest that it probably: (1) controls the flow of urine and thereby regulates water balance, (2) influences carbohydrate metabolism, and (3) has something to do with the onset of parturition. The neural connections among the supra-optic nucleus, tuber cinereum, and the mammillary bodies suggest that these structures may control, or at least influence, activity of the posterior lobe of the pituitary. Two substances with powerful pharmacologic effects, namely *oxytocin* and *vasopressin* (pitressin), have been extracted from the posterior lobe in fairly pure form. It is not known whether these substances are formed in the posterior lobe or are merely stored there after being secreted by the pars intermedia. The relatively crude extract, *pituitrin*, contains both fractions. Oxytocin acts primarily as a uterine stimulant and has little effect on the circulation. Vasopressin constricts the arterioles and capillaries and restricts the flow of urine. In man it does not raise the blood pressure significantly. Both substances

increase the concentration of sugar in the blood. The other pharmacologic effects produced by these substances are irrelevant for present purposes. Attempts have been made to correlate clinical syndromes, notably eclampsia, with hypersecretion of the posterior lobe, but the evidence presented is not convincing.

Diabetes insipidus.—The finest compilation of the fundamental knowledge regarding diabetes insipidus is that assembled by Fisher, Ingram and Ranson. It represents a summary of the outstanding work performed in the Institute of Neurology of the Northwestern University Medical School, together with a complete discussion of the studies performed in other laboratories. These have included an historical review and have summarized the position taken by two groups: (1) those who believe that diabetes insipidus is primarily a disturbance of the hypothalamus and (2) those who believe that it is primarily a disturbance of the hypophysis. The concept of Fisher, Ingram and Ranson will be quoted later.

The three authors referred to also reviewed work which suggests that the anterior portion of the hypophysis produces a *diuretic* hormone. The presence of this hormone was originally suggested by Crowe, Cushing and Homans in 1909. This concept has been studied during the intervening years, most recently by Richter, in 1934, and Pencharz, Hopper and Ryneerson, in 1936. Fisher, Ingram and Ranson also summarized evidence suggesting the rôle of the other endocrine glands, particularly the thyroid, in the metabolism of water. Their own views can be expressed best by a direct quotation:

"Our conception of the pathological physiology of diabetes insipidus can be stated as follows: The supraoptico-hypophyseal system regulates the secretion of the antidiuretic hormone by the neural division of the hypophysis. It should be emphasized that the neural division includes the infundibular stem and median eminence. The interruption of the supraoptico-hypophyseal tracts in the hypothalamus causes the neural division to become atrophic and functionally inactive . . . and leads to a deficiency of the antidiuretic hormone in the organism. Likewise, section of the stem high enough to cut all of it and the median eminence away from the hypothalamus brings about a similar atrophy and deficiency. Extirpation of

the neural division in all its parts leads to the same hormonal deficiency by virtue of the fact that it removes the site of formation of the antidiuretic principle. The evidence indicates that the antidiuretic hormone acts mainly on the kidney and prevents the secretion of excessive amounts of urine. The deficiency of this hormone, as a result of the types of damage described, brings about a primary polyuria which is followed by a secondary and compensatory polydipsia. The polyuria which develops can be thought of as representing the resultant of diuretic processes in the body unchecked by the antidiuretic mechanism. These diuretic processes are normally under the control of the pars anterior of the hypophysis and the polyuria may, therefore, be thought of as resulting from an uncompensated activity of this gland. In this sense, then, one may speak of diabetes insipidus as being caused by a disturbance of the equilibrium normally obtaining between the neural division and the pars anterior. It should be emphasized that we are speaking of an uncompensated activity of the pars anterior and not a hyperactivity. The pars anterior can be thought of as exerting its diuretic influence through its general control over metabolism and activity, rather than through a specific diuretic hormone. . . . It should be noted that we support the view that diabetes insipidus is essentially a hormonal disturbance, although the secretion of the antidiuretic hormone is under the nervous control of the hypothalamus. . . . Further, we have been led to conclude that the neural division itself and not the pars intermedia is the site of formation of the antidiuretic principle."

Not every patient who drinks large quantities of water and voids excessive amounts of urine has diabetes insipidus. For many individuals this is a manifestation of nervousness. The *differential diagnosis* can be made by testing the ability of the kidney to concentrate urine. A patient suffering from diabetes insipidus cannot concentrate urine to a specific gravity of more than 1.010 regardless of the number of hours he refrains from drinking fluids. A patient who has nervous polydipsia and polyuria has the normal ability to concentrate urine. Such a patient obviously should not be told the purpose of the test. He is simply told not to drink fluids of any sort for twelve hours and to save only the last specimen of urine which is

passed. Very few patients with diabetes insipidus, however, can stand to go this long without fluids.

Treatment for diabetes insipidus obviously consists of replacing the hormone which by its lack causes the disease. There are several ways of administering this hormone: hypodermically, by nasal spray and, more recently, by the use of powder. The value of the hypodermic injection of a solution of posterior pituitary extract in controlling the symptoms of diabetes insipidus was demonstrated independently in 1913 by Farini and Ceccaroni and by von den Velden. For the most part, the results of this treatment are satisfactory, but it causes certain disagreeable effects, such as pallor, headache, palpitation, and diarrhea. These may be eliminated by spraying the substance into the nose, as suggested by Blumgart. This method, however, is not always efficacious and it is expensive. Canelo and Lissner in 1935 found the cost of using such a spray to be between \$13.00 and \$15.00 per month.

In 1924, André and Lucie Choay suggested *nasal insufflation* of the dry, powdered substance obtained from the posterior lobe of the pituitary. This method has been found to be effective, more convenient, and less expensive than hypodermic injection. The average cost of using the powder is about \$2.00 per month.

The amount of powder which is necessary to control the symptoms of a patient with diabetes insipidus must be determined in each individual case. It has been our custom simply to have the patient obtain the powder and a glass tube and atomizer bulb. The patient measures the amount of powder on the end of a knife, places it in the end of the glass tube and blows it into the nose. The diabetes insipidus of many patients is controlled completely by insufflations in the morning and at bedtime. Some patients require more frequent insufflations; others are controlled with an insufflation once a day.

COMMENT AND CONCLUSIONS

Our lack of knowledge regarding the treatment of diseases caused by abnormal pituitary function is disappointing. A perusal of literature on this subject, however, would lead to the belief that our knowledge is fairly complete and that treatment is fairly well established. A good illustration that this is not

the case occurred at a recent meeting of neurosurgeons from medical centers all over the United States and Canada. These men have had an unusual opportunity to study patients suffering from tumors of the pituitary and from pituitary insufficiency as the result either of the tumor or the surgical removal of the offending tissue. This question was asked of this group: "Is there any one at this meeting who at any time has ever seen any patient helped by the injection of any anterior pituitary preparation yet available?" There was not a man at the meeting who would state that he had seen anything encouraging. This discussion, of course, does not apply to the results which are being obtained from the use of *ovarian* or *testicular* hormones, nor does it apply to those hormones which are obtained from *pregnancy urine* or *pregnant mares' serum*, which, although they are pituitary-like, are not actually pituitary hormones.

Finally, this discussion is not meant to reflect discredit in any way on the very excellent studies which are being carried on by many well-trained men in leading institutions. This work is most necessary and most valuable. What has been emphasized is that, at present, our lack of ability to treat disease of the pituitary is most discouraging.

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CHROMOPHOBE ADENOMAS OF THE PITUITARY GLAND

C. HUNTER SHELDEN

The clinical features produced by the chromophobe tumor represent a true compression syndrome, in contrast to the symptoms of the eosinophilic and basophilic adenomas which result from a specific hypersecretion.

The three structures usually involved by the pressure of an expanding primary intrasellar neoplasm are the *normal glandular tissue of the hypophysis*, the *bony and membranous confines of the sella turcica*, and the *optic chiasm*. Consideration of these various pressure features affords a satisfactory anatomic approach to the typical syndrome of this type of pituitary tumor.

Pressure on the normal glandular tissue.—Growth of the adenoma within the sella turcica gradually compresses the remaining glandular tissue and produces a slowly progressive reduction of pituitary function. The symptoms of hypopituitarism that ensue have previously been discussed in the article by Rynearson and Kepler.

Pressure on the confines of the sella turcica.—Headache is frequently a distressing early symptom. It is usually localized to the inferior frontal region near the midline on one or both sides. This type of headache differs in many respects from that caused by other tumors of the brain. It is not due to an increase in intracranial pressure, but results from stretching of the dural roof or diaphragma sellae. No doubt the many variations in the severity and duration of the headache may be traced to anatomic differences in this portion of the dura mater. Headache due to hydrocephalus of low grade may develop later if the tumor progresses to a size sufficient to cause partial compression of the third ventricle.

The two layers of the dura separate to enclose the pituitary gland within the sella turcica (Fig. 125). The outer layer lines the floor of the cavity, whereas the inner layer forms a roof over the pituitary fossa. That portion of the dura which is termed the "diaphragma sellae" exhibits numerous anatomic anomalies which are of clinical importance. Occasionally this membrane is almost entirely absent, leaving a wide outlet to the sella covered only by arachnoid; in such a case a pituitary tumor could rapidly expand upward without resistance.

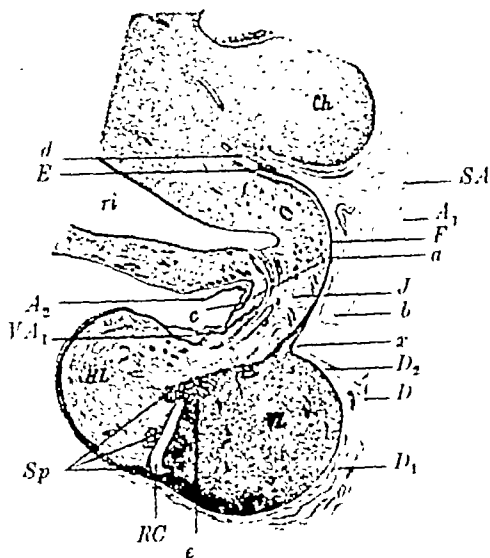


Fig. 125.—Sagittal section of normal pituitary gland illustrating its relation to adjacent structures: *D* indicates dura; *D*₂, diaphragma sellae; *Ch*, optic chiasm; *ri*, third ventricle.

Usually, the diaphragma sellae has a more or less complete and often dense roof which prevents an easy escape of a chromophobe tumor from the confines of the sella turcica. Thus, if this membrane is intact, the sella turcica becomes a closed cavity except for the small opening occupied by the pituitary stalk. Progressive enlargement of an adenoma within the sella produces not only glandular compression, but also erosion of bone. This erosion represents an attempt on the part of nature at decompression, and naturally occurs in the direction of

the least bony resistance. Thus the thin floor is decalcified early and the tumor gradually protrudes into the sphenoid air sinus, provided that this structure extends sufficiently in a posterior direction. The sella turcica becomes enlarged in all directions. The posterior clinoid processes are decalcified and eroded from before backward. During this gradual "ballooning" of the sella turcica, the superior tip of each posterior clinoid process is the last structure destroyed; hence, its presence associated with marked destruction of the sella is of diagnostic importance.

Growth of the tumor within the sella turcica may become unequal and may result in unilateral expansion and lateral extension of the tumor. Thus, complete unilateral destruction of the anterior and posterior clinoid processes may appear with only minimal changes on the contralateral side. The tumor, under such circumstances, may even present in the middle fossa of the skull. It is this type of unequal expansion that results in the bizarre symptomatology sometimes encountered among patients who have primary pituitary tumors. Impaired ocular movements may occur as the result of the lateral extension and impingement on the cranial nerves which traverse the cavernous sinus. Such a condition accounts for the presence of diplopia and ptosis, although these features are only rarely encountered. A chromophobe tumor which has reached a large size may even present in the middle fossa of the skull and produce symptoms referable to the temporal lobe. Under such circumstances there may be a history of epileptiform convulsions or gustatory hallucinations and not infrequently in such cases bilateral papilledema is also present.

The tumor, as long as it remains within the confines of the sella turcica, is essentially an epidural lesion, but once the diaphragma sellae ruptures, the tumor enters the subarachnoid space. Progressive enlargement of the tumor then produces compression of the optic chiasm and later may encroach on the anterior inferior portion of the third ventricle.

The degree of suprasellar extension cannot be determined by the usual roentgenographic methods unless calcification is present. In some clinics, particularly abroad, pneumoencephalographic or pneumoventriculographic studies are carried out routinely for all chiasmal lesions.

These operative procedures are of little diagnostic value except in those very rare cases in which bizarre neurologic signs are present. Pneumoventriculograms may be justified for a patient who has papilledema and evidence of increased intracranial pressure plus the usual signs of a chiasmal lesion; generally, a careful history alone will indicate the site of primary involvement. A patient who is too uncooperative for either obtaining a reliable history or a satisfactory perimetric field examination might require such diagnostic adjuncts, but, injury to the frontal lobe, due to a chromophobe adenoma, of such a degree as to cause the patient to be very uncooperative, is extremely uncommon. Pneumoencephalographic studies are of even less diagnostic value than pneumoventriculograms for this particular problem, because they seldom, if ever, afford localizing evidence which cannot be more easily determined by a careful examination of the perimetric fields.

Pressure on the visual pathways.—Every chromophobe adenoma of the pituitary gland will produce a disturbance of vision provided that the tumor attains sufficient size. However, the character of the visual defect depends more on the site of the optic chiasm and direction of growth of the tumor than on its actual proportions. Other factors such as the extent of cystic degeneration of the lesion and the occurrence of hemorrhage into the tumor play an important but secondary rôle in producing the loss of vision.

The presence of large arterial branches of the circle of Willis immediately adjacent to the optic nerves and chiasm is also of great importance in the production of the visual loss. This arterial network is generally depicted as having a constant pattern, but actually there exists no uniformity in number, caliber, or site of these vessels. Because of their position, the arteries most likely to account for damage to the visual pathways are the anterior communicating artery and the two anterior cerebral arteries. The latter vessels are probably of greater clinical importance than the former due to their large size and frequent anomalies.

Pressure exerted by an expanding pituitary tumor forces the optic nerves and chiasm upward against these large vessels and subjects them to the damaging effect of continued arterial pulsations. Not infrequently, as Kernohan has emphasized,



Fig. 126.—Arterial compression and notching of the optic chiasm. Note compression of chiasm between vessel and underlying tumor: *a*, appearance with vessel in place; *b*, grooving apparent after removal of the artery.

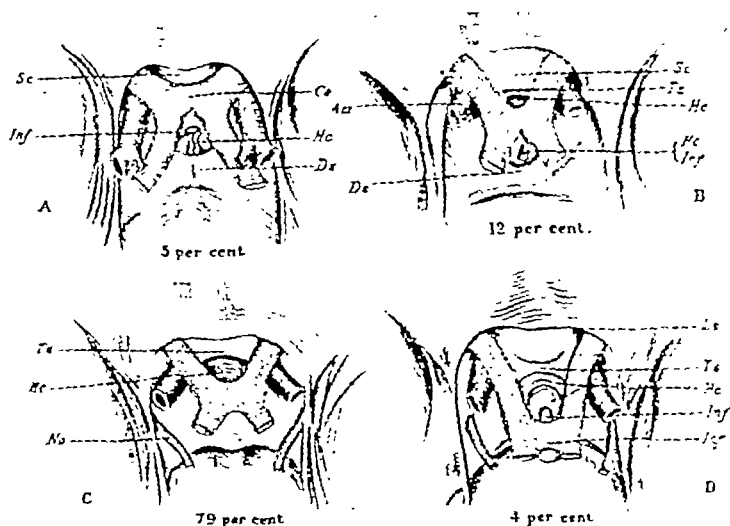


Fig. 127.—Anatomic variations in site of the optic chiasm. *A* represents optic chiasm far forward with short optic nerves. *B* and *C* represent intermediate positions. *D* represents an optic chiasm far posterior with long optic nerves. *Sc*, chiasmatic sulcus; *Inf*, infundibulum; *Co*, optic chiasm; *Hc*, hypophysis; *Ds*, dorsum sellae; *Ts*, tuberculum sellae; *No*, oculomotor nerve; *Ls*, sphenoidal limbus; *Aci*, internal carotid artery. (From Transactions of Ophthalmological Society of United Kingdom. De Schweinitz.)

there is visible on the superior surface of the optic chiasm, a distinct groove which represents the site of local destruction produced by one of these vessels (Fig. 126).

De Schweinitz called attention to the fact that the optic chiasm is not constant in its relation to the sella turcica (Fig. 127). In 5 per cent of cases, the chiasm is far forward near the sulcus chiasmaticus of the sphenoid bone. In such instances, the intracranial extent of the optic nerves is extremely short. In contrast to this, it was found that in 4 per cent of cases, the optic chiasm was situated far posterior over the dorsum sellae. Such patients necessarily had long optic nerves.

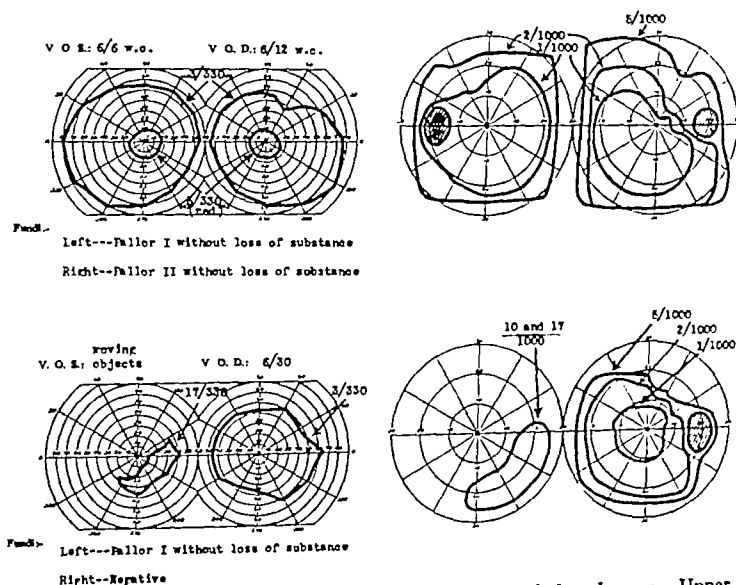


Fig. 128.—Early visual field defects due to a chromophobe adenoma. Upper diagram represents early bilateral upper-outer quadrant depression. Lower diagram shows early chiasmal changes due to chromophobe adenoma with evidence of prechiasmal involvement in the left eye. Note marked reduction of vision in this eye.

It is obvious that if the optic chiasm is far anterior, a pituitary tumor would present posterior to the chiasm between the optic tracts. Likewise if the chiasm were far posterior the tumor would present anterior between the optic nerves and might attain considerable size before the chiasm would be involved.

The great majority of patients possess an optic chiasm so situated that it becomes compressed in the early stages of development of a pituitary tumor. The most common defect of

the visual field typical of an early chiasmal lesion is a bilateral upper-outer quadrant depression for small test objects (Fig. 128). These changes are most readily demonstrated on the tangent screen at 1 or 2 meters. The defects progress clockwise in the field of vision of the right eye, and counterclockwise in the field of vision of the left eye. In some instances the bitemporal defect is at first of scotomatous type. The charac-

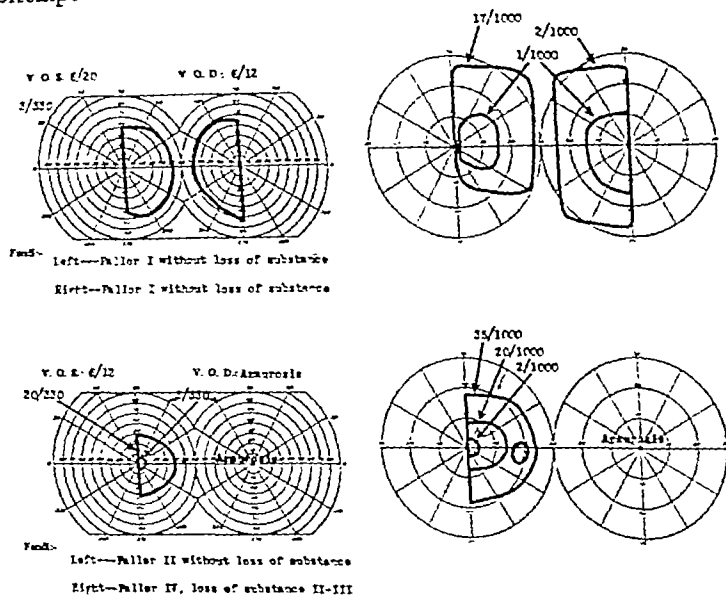


Fig. 129.—Perimetric field defects associated with well-advanced chromophobe adenoma. Upper diagram represents complete bitemporal hemianopia with some evidence of involvement of the inferior nasal field in the left eye. Lower diagram shows advanced stage of chromophobe adenoma producing amaurosis on the right and complete temporal hemianopia on the left. Note marked fundusoscopic changes in the right eye.

teristic defect of a well-advanced tumor is a bitemporal hemianopia which at first is relative but later becomes absolute or dense to a test object of any size (Fig. 129). A bitemporal defect as such may persist for a long period of time, but if the pressure continues, the nasal fields will become involved and blindness will ensue.

A tumor which presents well anterior to the optic chiasm between the optic nerves produces a prechiasmal type of defect

of the visual fields, the essential feature of which is an early loss of central vision which is usually unilateral owing to the presence of a central scotoma (Fig. 128). As the tumor enlarges, the optic chiasm itself becomes affected. The result is the usual bitemporal type of hemianopia plus the original central or cecocentral scotoma. The late result of such a process is usually amaurosis in one eye and a temporal hemianopia in the other (Fig. 129).

A chromophobe tumor which presents posterior to the optic chiasm between the optic tracts may produce a bitemporal hemianopia provided that the lesion remains adjacent to the chiasm with the bulk of the growth essentially in the midline. However, irregular extension may easily produce pressure on the optic tract on one side with a resultant homonymous hemianopia, usually of incongruous type.

In the early phases of pressure on the chiasm and optic nerves by a pituitary tumor, the optic disks usually appear normal ophthalmoscopically. Later pallor is visible and, still later, loss of substance which gives rise to the appearance of simple optic atrophy. Papilledema is rarely seen in association with pituitary tumors. It should be borne in mind that papilledema is not likely to develop in the presence of a definite degree of optic atrophy, even though subsequent enlargement of the tumor produces a great increase in intracranial pressure.

The *prognosis* with regard to visual improvement following operation should be based on the ophthalmoscopic appearance of the optic disks rather than on the extent of the defect of the visual fields. The presence of visible loss of substance or atrophy of nerve tissue is an unfavorable sign.

To establish the *diagnosis* of a chromophobe adenoma of the pituitary gland, one must depend almost entirely on the presence of characteristic roentgenographic and ophthalmologic changes and not on the mere clinical evidence of hypopituitarism. Many patients who have advanced lesions will show very little evidence of pituitary dysfunction. Occasionally, however, the signs of hypopituitarism furnish the only clue that will lead to the establishing of the diagnosis by the method already discussed. If other evidence suggests the diagnosis of a chromophobe adenoma of the pituitary gland a low systolic blood pressure may be a significant clinical finding. This is

of some diagnostic value because it is seldom present in patients having chiasmal lesions which are not essentially of pituitary origin.

Differential diagnosis.—A variety of lesions near the optic chiasm may produce symptoms and clinical signs which simulate those which result from a pituitary adenoma. The majority of these lesions, in their typical form, are associated with certain characteristics which allow easy distinction between them and the usual chromophobe adenoma.

Eosinophilic tumors of the pituitary gland may present changes in the roentgenogram and in the perimetric fields similar to those of chromophobe adenoma, but the acromegalic features associated with the eosinophilic type render the differential diagnosis simple. Generally, the diagnosis of acromegaly in well established cases can easily be made merely by examination of the roentgenograms of the skull.

Basophilic adenomas practically never produce visual disturbances or roentgenographic evidence of a primary pituitary tumor. The clinical diagnosis, when made, is usually based on the general habitus of the patient and the presence of glycosuria, hypertension and the other classical signs of this rare condition (see article by Ryneerson and Kepler).

Intrasellar tumors that arise from residual cellular rests of the primitive hypophysial duct present the greatest difficulty in differential diagnosis. This type of neoplasm has been termed "hypophyseal duct tumor," "adamantinoma," "suprasellar cyst," "Rathke pouch cyst," and "craniopharyngioma." All of these terms have been coined to designate a common tumor of congenital origin. These tumors arise predominantly in children or young adults. Roentgenologic evidence of suprasellar calcification of varying degree is evident in approximately 75 per cent of cases. In all other respects, they are indistinguishable clinically from chromophobe adenomas of the pituitary gland. Papilledema occurs more frequently in association with suprasellar than with intrasellar tumors.

Meningiomas of parasellar origin generally are associated with an older age group than are primary intrasellar tumors. They often present evidence of local bony proliferation and increased local vascularity of the skull.

Primary tumors of the optic nerves or optic chiasm usually

produce a very rapid loss of vision with bizarre changes in the visual fields. Enlargement of the optic foramina may often be demonstrated roentgenologically.

Vascular lesions near the optic chiasm may produce visual disturbances. Local erosion of bone by or calcification within an aneurysm of the circle of Willis or of the internal carotid artery may be revealed roentgenographically. Bizarre lesions of the midbrain must be considered as well as local inflammatory reactions that produce a chronic chiasmal arachnoiditis.

Brain tumors, particularly those situated in the posterior fossa, at times may produce bitemporal hemianopia and thus closely simulate a primary pituitary lesion. The bitemporal type of defect of the visual fields in such cases is the result of a great increase in intracranial pressure with hydrocephalus. The anterior portion of the dilated third ventricle exerts marked downward pressure on the optic chiasm. A careful chronologic history from such patients will reveal that the headache and evidence of increased intracranial pressure long preceded the onset of changes in the perimetric fields.

The differential diagnosis of *hypopituitarism* has been discussed elsewhere (Ryngerson and Kepler).

Treatment.—Treatment is strictly surgical. Palliation results in progression of the defects of the visual fields as well as subsequent development of pallor and loss of substance of the optic disks. *Roentgen therapy* has been advocated, but this is a dangerous procedure except for properly selected patients who may be carefully observed at frequent intervals. All too often, during the period of palliation, irreparable changes occur in the optic nerves which result in eventual blindness.

MEDICAL MANAGEMENT OF DISEASES OF THE THYROID GLAND

AUSTIN C. DAVIS AND L. P. HOWELL

Classification.—The following classification of thyroid disease, as devised by H. S. Plummer¹ and adopted at The Mayo Clinic, will be followed in this discussion:

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| 1. Diffuse colloid goiter. | } Types or stages of endemic goiter. | } Hyperthyroid states. |
| 2. Adenomatous goiter without hyperthyroidism. | | |
| 3. Adenomatous goiter with hyperthyroidism (secondary hyperthyroidism). | | |
| 4. Exophthalmic goiter (Graves' disease, Basedow's disease; primary hyperthyroidism). | } Hypothyroid states. | |
| 5. Myxedema (Gull's disease in adults). | | |
| 6. Cretinism. | | |
| 7. Malignant disease of the thyroid. | | |
| 8. Thyroiditis, acute and chronic. | | |
| 9. Parasitic and fungous diseases of the thyroid. | | |
| 10. Congenital anomalies. | | |

Differential diagnosis.—We wish to emphasize the medical treatment of the more common diseases of the thyroid gland. At the outset, however, it is desirable to mention difficulties which commonly arise in differential diagnosis, particularly as they will affect treatment and prognosis. These difficulties usually rest between diffuse colloid goiter and exophthalmic goiter, the adenomatous goiters with hyperthyroidism and without hyperthyroidism, any type of goiter and a psychoneurotic state, and hypertension associated with elevated basal metabolic rates. Less commonly one is confronted with difficulty in the differential diagnosis of carcinoma of the thyroid gland, adenomatous goiter, exophthalmic goiter, and thyroiditis. Thus thyroidectomy may be performed without necessity in cases of diffuse colloid goiter or psychoneurosis, or the benefit of surgery may be unwittingly denied the patient when otherwise indicated. The minimal risks now associated

with the surgical treatment of thyroid disease can be improved, let alone maintained, only by making an accurate diagnosis. This requires vigilance. Further, the patient deserves an accurate *prognosis* as well as an accurate diagnosis. He needs to know not only what the treatment will accomplish, but also what it will not accomplish. For example, the removal of an adenomatous goiter without hyperthyroidism may be justified as a prophylactic measure, but the patient must be thoroughly informed so that he will not expect such an operation to relieve him of symptoms which are psychoneurotic in origin.

Therapy.—Except for diffuse colloid goiter and the hypothyroid states, the treatment of thyroid disease usually requires the consideration of *surgical intervention*. The latter is the procedure of choice in all cases of hyperthyroidism and in selected cases of adenomatous goiter without hyperthyroidism, carcinoma of the thyroid gland, and thyroiditis. Radiation therapy has its enthusiastic supporters and is used not only for the treatment of carcinoma of the thyroid gland, but also for that of hyperthyroid states as well, especially for exophthalmic goiter.

We feel that *radium* or *roentgen therapy* is to be used in many cases of malignancy of the thyroid gland, but we do not share the opinion that these measures are the treatment of choice for the hyperthyroid states. We doubt that radiation therapy accomplishes anything in cases of adenomatous goiter with hyperthyroidism. We do resort to its use in exceptional cases of exophthalmic goiter, in which operation, for some reason, is definitely contraindicated.

The *medical treatment* of thyroid disease is directed toward the prophylaxis of goiter, the management of diffuse colloid goiter, the hypothyroid states, selected cases of thyroiditis and carcinoma of the thyroid gland and is utilized in preoperative and postoperative care. In this discussion we will not attempt to describe or evaluate the technic of operations on the thyroid gland.

Inadequate *iodine* intake is apparently the most goiterogenic factor and will be the only one that we shall discuss. The use of iodine for the prophylaxis of endemic goiter has been well established in this country by Marine and Kimball.¹⁰ The suitability of using iodized salt for this purpose is obvious and

it is effective. The practice of iodizing salt presents two problems: first, the amount of iodine to be contained in salt; second, the advisability of making mandatory the use of iodized salt. The recommended amount of iodine in salt deemed as a desirable prophylaxis varies. Eggenberger, of Switzerland, has written: "Iodization of salt for the prevention of goiter is (a) recommended in doses of one part of potassium iodide to 100,000 parts of cooking salt, if *all* cooking salt which is to be used for human food consumption can be iodized, or (b) doses of one part of potassium iodide to 10,000 parts of salt if only the fine table salt can be iodized." Kimball advised that for the future "iodized salt in this country be standardized at .01 per cent or one part sodium iodide to 10,000 parts of salt." Marine suggested a concentration of one part of potassium iodide to 100,000 parts of salt.

Studies by McClure indicate that the sales of iodized salt are tending to drop in Michigan and that there may be a corresponding increase in the incidence of goiter. Such tendencies may be offset only by propaganda or mandate. It is not within the province of this discourse to choose between such alternatives but the doctor must not lose sight of the problem and its possibilities.

DIFFUSE COLLOID GOITER

Diffuse colloid goiters of any appreciable size occur rarely after the second or third decade of life. They are most common in adults during pregnancy. They are mainly, if not entirely, the result of the morphologic response of the thyroid gland to an *inadequate supply of iodine*. The gland usually responds to the use of iodine by diminishing in size.

Formerly, huge colloid goiters in adolescents were not infrequently seen at the Clinic. These were treated, usually, with thyroxin or desiccated thyroid gland followed by iodine. Rarely was operation necessary. Today, these huge colloid goiters of adolescence are seldom seen. Although we question whether the usual case of small diffuse colloid goiter as now seen needs more iodine than is prescribed as a goiter prophylaxis in individual cases, we usually do prescribe more than prophylactic amounts which can be given in any convenient form. Specially prepared chocolate tablets containing 0.01 gm. of iodine are commonly given once a week. Means has

suggested the use of 1 drop of liquor iodi compositus (U.S.P.) a week as an individual prophylactic against goiter. This contains 1.7 mg. or 1,700 gammas of iodine. The suggested amounts of iodine in iodized salt have already been given.

ADENOMATOUS GOITER WITHOUT HYPERTHYROIDISM

If adenomatous goiters without hyperthyroidism contain relatively large amounts of colloid, some diminution in size may follow the ingestion of iodine, but the adenomas remain. We believe that occasionally hyperthyroidism will occur with such goiters following the use of therapeutic amounts of iodine over long periods of time. Although such a danger does not manifest itself frequently, we agree with Means that iodine does no good in these cases and therefore it should not be used. There is no curative medical treatment.

The treatment of choice for asymptomatic adenomatous goiter is *thyroidectomy*. There is but one reason for this, namely to prevent possible trouble such as hyperthyroidism, carcinoma, or obstructive dyspnea in the future. The operability of these goiters is determined by the patient's age and by the size of the goiter. Unfortunately there are no data, so far as we know, which enable the physician to forecast with any degree of accuracy the likelihood of a nontoxic adenomatous goiter becoming toxic. Pemberton noted that, at The Mayo Clinic, the ratio of operative malignant tumors to the operative benign nodular goiters has risen from 2 per cent in 1919 to 4.9 per cent in 1937. In 60 per cent of the operative cases of malignancy of the thyroid, the malignancy was not suspected before operation. Thyroidectomy is the treatment of choice in all cases of *substernal* and *intrathoracic* goiter.

An adenomatous goiter, whether it is hyperfunctioning or not, may produce local symptoms of pressure on the trachea which sometimes are profound enough to cause obstructive dyspnea. Such local symptoms are always an indication for thyroidectomy. Needless to say, these symptoms are easily confused with those of globus hystericus. Venous obstruction may be present and is another indication for thyroidectomy. Dysphagia may be a symptom. One of us (Davis) has observed, however, that when the dysphagia is so troublesome as to be the patient's chief complaint, it is imperative to exclude

causes other than goiter. Rarely does a goiter produce severe dysphagia.

The *indications* for thyroidectomy are governed by the patient's age and the physical characteristics of the goiter. Prior to the fourth decade, resection of the thyroid gland is more likely to be followed by recurrence of the goiter than it is later on. It is a comparatively safe rule to advise observation of the goiter prior to the age of thirty years and thyroidectomy after that age. It is to be kept in mind, however, that carcinoma of the thyroid gland may occur at any age.

Aged persons can hardly be urged to undergo thyroidectomy for nontoxic adenomatous goiters; however, the older the patient the sharper the observation must be to exclude early evidences of hyperthyroidism or carcinoma.

The physical characteristics of the adenoma or adenomas will influence the decision to resort to medical or surgical management. Tiny adenomas that just admit of detection are usually not carcinomatous; however, it is unwise to rely implicitly on such a generalization. We have seen thyroid glands containing but a single adenoma, 1 cm. in diameter, undergoing malignant change. At the Clinic we use the rule of thumb principle, that an adenoma 1 in. (2.5 cm.) or more in diameter warrants thyroidectomy; the management of smaller adenomas will depend on other less objective criteria. A strong suspicion of malignancy may justify operation in these cases. In determining whether operation should or should not be performed for goiters in borderline cases, we have always considered that the more the goiter conforms to a discretely nodular tumor, as contrasted with a symmetrically enlarged gland, the smaller it need be to warrant surgical removal.

The preoperative preparation of these patients is directed toward the establishment of maximal health. If one has excluded or controlled other co-existing systemic disease the patient rarely needs other specific preoperative medical treatment.

ADENOMATOUS GOITER WITH HYPERTHYROIDISM

Thyroidectomy, unless absolutely contraindicated, is the treatment for adenomatous goiter with hyperthyroidism and should be performed without unnecessary delay. When some other surgical procedure is also indicated, as for example for

carcinoma elsewhere in the body, thyroidectomy should nearly always take precedence. Not infrequently it will be observed that hyperthyroidism aggravates other stresses or disease, such as gallbladder disease, peptic ulcer, diabetes, or heart disease. Cure of the hyperthyroidism is one of the first steps to be taken for such afflictions. The preoperative medical management of adenomatous goiter with hyperthyroidism is, of course, directed toward the prevention of complications and the maintenance of optimal health. Those problems which in our experience arise most commonly during medical management will be considered separately and for convenience can be grouped under preoperative and postoperative care.

Preoperative medical management.—THE USE OF IODINE.—We give iodine in the form of Lugol's solution (10 drops three times a day for several days) in the preoperative treatment of adenomatous goiter with hyperthyroidism for two reasons: In 11.3 per cent of all clinically diagnosed adenomatous goiters, the pathologist found the goiter to be entirely of the exophthalmic variety.⁶ The use of iodine in these cases will be considered subsequently. Thus, the routine use of iodine will protect the patient against unsuspected exophthalmic goiter and all of its attendant dangers. The other reason for using iodine preoperatively is that, in some of these cases, it seems to exert a beneficial effect on the disease. Although not recognizing exophthalmic goiter and adenomatous goiter with hyperthyroidism as different diseases, Coller and Potter and Means have expressed the belief that iodine exerts a beneficial effect on both of these diseases. These authors observed that iodine is more helpful in cases of exophthalmic goiter than in cases of adenomatous goiter.

COMPLICATIONS.—Toxic goiter can cause cardiac failure or it can aggravate an independent cardiopathy. In either case, the rôle of goiter may be overlooked. It is not unusual for patients with hyperthyroidism to consult a physician for the first time only when the heart has failed. Insidious symptoms of hyperthyroidism may have been present for years, but the calamitous symptoms of resulting congestive heart failure were necessary to bring them to medical attention. It is wise, therefore, to make doubly sure of the etiology in any case of congestive heart failure or arrhythmia lest a state of

hyperthyroidism be overlooked. We shall concern ourselves with three comparatively common cardiac complications in thyroid disease. They are: arrhythmias, angina pectoris and congestive heart failure.

Auricular fibrillation is the most common arrhythmia associated with hyperthyroidism. It appears in about 25 per cent of all cases. "It is present as a persistent mechanism in about 10 per cent of the cases; it appears in a paroxysmal manner, with rapid rate, in about 5 per cent of the cases and it occurs intermittently, without unduly rapid rate, ultimately disappearing after the arrest of the disease, in about 10 per cent of the cases. The persistence of auricular fibrillation following thyroidectomy is suggestive of the presence of associated primary cardiac disease, residual cardiac injury from protracted hyperthyroidism or recurrent hyperthyroidism of exophthalmic goiter."¹⁰ Unless congestive heart failure is present, the auricular fibrillation rarely requires special preoperative treatment. Auricular fibrillation alone should never be a contraindication of thyroidectomy.

Auricular flutter is encountered infrequently. If this arrhythmia persists after several days of rest and iodination, the use of quinidine to stop the flutter is to be considered before proceeding with thyroidectomy. If it is considered unwise to give quinidine, or if the flutter persists despite real effort to convert the rhythm by using digitalis and quinidine or quinidine alone and if there is no evidence of congestive heart failure, it becomes necessary to proceed with thyroidectomy.

Haines and Kepler pointed out that the risk of thyroidectomy in cases of *angina pectoris* associated with hyperthyroidism usually is not sufficiently great to be a contraindication to operation. Definite improvement in the anginal syndrome was noted in many of their cases. We believe that the association of angina pectoris with goiter is usually an indication for thyroidectomy. Our experience with total thyroidectomy for coronary disease has not been encouraging.

Except possibly for the use of digitalis, the preoperative treatment for *congestive heart failure* associated with hyperthyroidism is the same as in any case of primary heart failure. Physical rest alone in these cases may restore cardiac sufficiency and should be given a thorough trial. The diuretics,

such as potassium nitrate and the mercurials, are very helpful and unless definitely contraindicated can be used as a supplement to rest. If, after a thorough trial, these measures fail to restore adequate circulation, or if rapid fibrillation persists, digitalization may be advisable. Whenever we can, and we usually can, we allow the patient to compensate *without the aid of digitalis*. Our reluctance to use digitalis regularly in such cases is based on the strong impression that its *routine use* increases rather than decreases the risk associated with thyroidectomy. If for various reasons it appears necessary to use digitalis the administrations should be stopped a few days before thyroidectomy to preclude any cumulative effect in the tissues. The achieved cardiac compensation should be maintained for at least a few days before undertaking thyroidectomy. During this time, the patient should be able to be "up and around" for four to six hours a day without evidence of decompensation. We believe that such a regimen assures a more adequate stamina for operation than would exist if the patient had been kept in bed continuously until the time of operation. It also affords a practical test of cardiac reserve. The reappearance of heart failure would definitely contraindicate operation temporarily.

True *diabetes* is not a rare complication of hyperthyroidism. At The Mayo Clinic, Wilder found that it occurred in 1.1 per cent of the cases of hyperthyroidism and in more than half of the cases in which it occurred it had existed previous to the onset of the hyperthyroidism. The appearance of hyperthyroidism invariably aggravates the severity of the diabetes and recovery from the hyperthyroidism is accompanied by improvement in the severity of the diabetes.

The treatment of hyperthyroidism complicated by moderate or severe diabetes mellitus raises problems that do not arise during the management of either disease alone, owing to the fact that each disease intensifies the ill effects of the other. Inasmuch as the modern treatment of diabetes is much more flexible so far as details are concerned, as compared to the treatment of hyperthyroidism, it is advisable to modify the standard treatment of diabetes to meet the peculiar needs of the patient with hyperthyroidism. The diet, therefore, should be extremely liberal in its total caloric and carbohydrate con-

tent. It should contain at least 1 gm. of protein per kilogram of body weight (based on the ideal and not the actual weight of the patient), and we have seen no ill effects following the use of diets that contained considerably more protein. One of our recent patients was given 400 gm. of carbohydrate, 125 gm. of protein and sufficient fat (210 gm.) to bring the total calories up to approximately 4000. In planning such a diet it is necessary to use some sugar or foods containing sugar if the bulk of the diet is to be kept within reasonable limits.

Sufficient insulin should be given to keep the urine approximately sugar free. At first the insulin requirements are likely to be high. If the patient happens to have an exophthalmic goiter a decrease in the requirements for insulin may be expected and should be anticipated when the effects of the administration of Lugol's solution begin to appear. Operation should be delayed until the diabetes has been well controlled for at least a week or ten days. Regular insulin is the remedy of choice unless the physician has had considerable experience with the use of protamine-zinc insulin. The amount of insulin administered should be reduced about 50 per cent on the morning of the operation. Subsequently the amount of insulin that is necessary will depend on the degree of glycosuria and the concentration of the sugar in the blood. An increase in the insulin requirements can be anticipated beginning about forty-eight hours after the operation and continuing for several days thereafter. When the patient's temperature has returned to normal, the necessary dosage of insulin begins to decline. During convalescence the dosage of insulin often can be decreased arbitrarily even though a small amount of sugar is still present in the urine. Usually at the end of three weeks most of the beneficial effects of thyroidectomy are apparent so far as the insulin requirements are concerned and by that time the degree of severity of the patient's residual diabetes and his insulin requirements can be evaluated.

If diabetes first appears during the course of hyperthyroidism, the patient probably has had pre-existing latent diabetes which under ordinary circumstances would not have become manifest. Following control of the hyperthyroidism by successful thyroidectomy, the severity of the diabetes is

ameliorated and may even regress to a subclinical or latent level.

Pregnancy does not contraindicate thyroidectomy for adenomatous goiter with hyperthyroidism. The fear of causing the patient to abort should not deter the surgeon, as spontaneous miscarriages are prone to occur when hyperthyroidism is uncontrolled.

Postoperative medical management.—**COMPLICATIONS.**—The most important postoperative complications of thyroidectomy which we will consider are pneumonia, heart disease and respiratory obstruction with anoxemia. Postoperative parathyroid insufficiency has been considered in the article on parathyroid insufficiency.

We believe that at present sulfapyridine is the treatment of choice for *pneumonia*. Oxygen may be desirable as a supplement, depending on the extent of the pneumonia and on the degree of toxemia and cyanosis. The use of oxygen will be considered later.

Auricular fibrillation that appears postoperatively usually disappears spontaneously. This may also be true in the case of *auricular flutter* which is less common than auricular fibrillation under such circumstances. It is seldom necessary to attempt conversion to normal rhythm in any case within six weeks after operation. Unless *congestive failure* is imminent, we believe that the patient should be given every opportunity to achieve this normal rhythm spontaneously. Quinidine should be reserved for those comparatively few cases of fibrillation with postoperative congestive heart failure in which use of the drug is not contraindicated.

Respiratory obstruction with anoxemia is not an unusual complication and may arise from several causes: injury to the recurrent laryngeal nerves with paralysis of one or both vocal cords, edema of the larynx or of surrounding structures, tetany with laryngospasm, postoperative hemorrhage and occasionally tracheal collapse. The last two complications are primarily surgical. Hemorrhage sufficient to produce obstructive symptoms requires evacuation of the clots and ligation of the bleeding points. Injury to the recurrent laryngeal nerves with paralysis of the vocal cords may be due either to accidental section of the nerve, to trauma to an intact nerve by

operative manipulation or to edema of the contiguous structures. In case of the latter involvement, the function of the nerve gradually returns as the reaction to the trauma subsides. In case of severe obstructive edema, arrangements should be made for tracheotomy and a tracheotomy set should be kept in the room. Tracheotomy may often be rendered unnecessary by the administration of oxygen or preferably of oxygen and helium.

Following the studies of Haines and Boothby,⁶ we use *oxygen therapy* for all patients who present evidence of anoxemia after thyroidectomy. Anoxemia occurs in association with pneumonia, respiratory obstruction and certain cases of congestive heart failure and pulmonary edema. The clinical appearance of these entities during the first three or four postoperative days certainly justifies the use of oxygen therapy; however, anoxemia as evidenced by progressive cyanosis and dyspnea should be watched for and if found the immediate use of oxygen is advisable, even though there is no other evidence of pulmonary embarrassment.

In cases of *tracheal obstruction* resulting from edema or in cases of cord palsy helium and oxygen together (60 to 80 per cent helium and 20 to 40 per cent oxygen) can be used. Sometimes this procedure will preclude the need of doing a tracheotomy. The oxygen can be given by the tent method or by the new mask inhalation method. The oxygen and helium mixture is preferably given via the mask method. Parathyroid insufficiency as mentioned previously will be discussed elsewhere.

EXOPHTHALMIC GOITER

There are exceptional cases of exophthalmic goiter in which a good response occurs to medical management alone. Such cases are usually mild in degree. There are also some cases of recurring exophthalmic goiter which do not require operation and which will be considered separately later. The major part of this discourse, however, is based on the premise that *thyroidectomy* is usually the procedure of choice for exophthalmic goiter. For convenience we will divide our discussion of this problem into the preoperative and postoperative medical management, just as we did with adenomatous goiter with hyperthyroidism. These two diseases present many identical

problems or complications from the standpoint of management. In general, the management of complications, such as heart disease, pneumonia, diabetes, pregnancy and respiratory obstruction, is the same in cases of exophthalmic goiter as in those of adenomatous goiter with hyperthyroidism. We will try, however, to emphasize those aspects of these problems which are unique to exophthalmic goiter.

Spontaneous remissions.—It is well to bear in mind, in considering the treatment of exophthalmic goiter, that this disease characteristically follows a very irregular course. The course is one of spontaneous exacerbations and remissions in severity of varying duration. A remission may be partial with the individual continuing to suffer from a less severe degree of hyperthyroidism or it may be complete with restoration of health. A complete remission may be permanent or may persist for months or years and be followed by an exacerbation of the disease. This natural tendency of the disease has led, in the past, to some confusion regarding the efficiency of various therapeutic measures which have been advanced. Cures, which were in reality spontaneous remissions, have been attributed to the treatment which was being employed at the time.

Preoperative medical management.—**IODINE.**—The beneficial effect of iodine on the course of hyperthyroidism has been noted repeatedly and by various observers. H. S. Plummer,¹⁷ in 1923, undertook a further investigation of the problem and administered adequate amounts of iodine to a large series of patients. He found that patients with exophthalmic goiter responded to this treatment with a pronounced decrease in the severity of the disease, a drop in the basal metabolic rate and a marked fall in the postoperative mortality rate. This experience thoroughly established the importance of iodine in the treatment of exophthalmic goiter.

At The Mayo Clinic the routine dose of iodine which has been employed is 10 drops of liquor iodi compositus, U.S.P. (Lugol's solution) three times daily. It is administered after meals and in an ounce of water, milk, or grape juice, the last two being effective in disguising the taste of the iodine. Ordinarily, a definite improvement is noted in four or five days. This consists in a decrease in the degree of nervous stimulation. The patient becomes more calm and the semi-purposeful move-

ments and physical restlessness so characteristic of the more intense phases of exophthalmic goiter stimulation decrease. This is accompanied by an increase in the muscular strength and a feeling of well-being and relief from nervous strain. There is a decrease in the pulse rate, the pulse pressure is lowered, and the active pulsation of the cervical vessels becomes less apparent.

The appetite is favorably affected. In those cases in which the appetite is ravenous, the intense hunger is usually mitigated and in those cases in which there is nausea or vomiting, these symptoms are relieved and the intake of food is increased. Gastro-intestinal crises are usually well under control on the fifth day of administration of iodine. The patient becomes less intolerant to heat, there is a decrease in the basal metabolic rate, excessive perspiration becomes less troublesome and the tremor, which is often a prominent symptom, subsides.

The improvement is usually most noticeable between the seventh and the tenth days. It is not unusual, however, for the patient to continue to improve over a much longer period, often two to three weeks. At times a definite progressive improvement in general health occurs over a period of several months. This is particularly true of markedly debilitated individuals who have exophthalmic goiter of long duration and probably indicates a gradual process of repair following relief from the more severe degree of intoxication.

The question of the administration of iodine to individuals over *long periods* of time has been the subject of some controversy. In certain individuals improvement is found to occur up to a certain point, beyond which no further improvement occurs and the condition remains stationary. In others, after a period of symptomatic improvement, an increase in the degree of hyperthyroidism occurs with further elevation of the basal metabolic rate. Some observers have felt that such patients have become tolerant to iodine and that withholding iodine for a period of time, followed by a resumption of its use, would result in further improvement. Our experience has been that the withdrawal of iodine after an *initial period* of improvement is followed by an aggravation of the symptoms in from one to three weeks. Subsequent administration of iodine will again control the symptoms, but not to any greater degree than

in the first place. It would seem that no benefit is derived from the temporary withdrawal of iodine, and the patient usually is subjected for a period of time to an increase in the intensity of his illness with its attendant dangers. The general rule to be followed is that the patient should receive iodine as long as he has exophthalmic goiter and for some time thereafter.

The question of operation on patients who have received iodine over protracted periods is often encountered. This circumstance does not contraindicate operation, provided that other conditions are satisfactory. In fact, such patients usually tolerate operation remarkably well, often in spite of high basal metabolic rates. This should not be misinterpreted, however, as an advocacy of the administration of iodine over protracted periods if this can be avoided. Once a satisfactory effect has been obtained with iodine and there are no surgical contraindications, delay of operation only serves to prolong the period of morbidity and incurs the risk of increasing hyperthyroidism and intercurrent disease. It is to be borne in mind that the duration of the disease is an important factor in the surgical mortality. Occasionally, and usually in mild cases with relatively low elevations of the basal metabolic rate, the administration of iodine will be accompanied by a drop of the basal metabolic rate to within normal limits. It is not unusual for this drop in the basal metabolic rate to be associated with complete relief from all evidences of the disease. If such control can be maintained by the continued administration of iodine, the clinician is tempted to delay operation, hoping for a spontaneous remission to occur. Such a policy may be permissible in a limited number of cases if the patients can be kept under close supervision, for with an abeyance of all symptoms any progressive visceral damage, if present, must be slight. However, the danger of an exacerbation is present and the optimal time for operation may be missed. In this connection, it is well to point out that the basal metabolic rate cannot be accepted as the sole criterion of activity of the disease. Individuals with basal metabolic rates within normal limits may still present distinct evidence of activity of the disease. For such individuals, the normal basal metabolic rate may be well below the usual average.

On the whole the most satisfactory *rule* to follow is that if the continued administration of iodine is necessary to control the disease and the withdrawal of iodine results in a prompt return of the symptoms, resection of the thyroid gland is indicated.

The effect of iodine on the *exophthalmos* is not so striking as it is on most other manifestations of exophthalmic goiter. It is probable that the continuous administration of adequate amounts of iodine established early in the course of the disease is an effective means of preventing or delaying the appearance of this symptom. Once exophthalmos has appeared, however, the administration of iodine does not produce, as a rule, any marked regression in the actual prominence of the eyes. Certain of the accessory ocular signs may be decreased, however, and this may diminish the appearance of exophthalmos, although the actual degree of ocular protrusion as measured by the exophthalmometer may be unchanged. The width of the palpebral fissure may be decreased to such an extent that the sclera no longer shows above the iris, rendering the appearance of the eyes more nearly normal. The "stare" so characteristic of patients highly stimulated owing to exophthalmic goiter is greatly decreased.

A review of the foregoing observations indicates that the improvement following the use of iodine in exophthalmic goiter is manifested in two ways: (1) by lowering the basal metabolic rate and (2) by amelioration of those symptoms that are peculiar to exophthalmic goiter, particularly the tendency toward crisis. The latter manifestation occurs whether or not the height of the basal metabolic rate is favorably influenced. It is chiefly owing to this effect that the introduction of iodine in the preoperative treatment of exophthalmic goiter produced such a dramatic fall in the surgical mortality. Previous to the introduction of iodine therapy the greatest danger following operation was fatal hyperthyroid crises; with preoperative iodination these reactions are almost entirely prevented.

REST.—The value of rest in the treatment of exophthalmic goiter can hardly be overemphasized, and this applies to freedom from mental cares and responsibilities as much as it does to physical relaxation. The amount of time that the patient should spend in bed varies greatly with the individual patient,

depending on such factors as the severity of the hyperthyroidism and the presence of myocardial insufficiency. Patients who have a mild degree of hyperthyroidism should have ten hours in bed and a rest period of one to two hours both in the morning and afternoon. In severe cases and particularly in those in which there is evidence of myocardial insufficiency more or less complete rest in bed should be prescribed until the symptoms are controlled. In cases of exophthalmic goiter, however, complete confinement to bed is attended with a marked loss of muscular strength, no matter how favorably it may affect other symptoms. An individual getting up from two or three weeks of complete rest in bed usually shows a severe degree of muscular weakness and may be practically unable to walk. This weakness disappears after a few days of increasing activity but until it does disappear the patient cannot be considered in condition for operation. The patient should be up and around from four to six hours daily for several days before the operation is undertaken.

Since, in cases of hyperthyroidism, the caloric need is greater than when a normal basal metabolic rate is present, the caloric intake should be adequate. Care should be taken to supply sufficient vitamins owing to their rapid exhaustion in the presence of increased metabolism.

COMPLICATIONS.—The treatment of the hyperthyroid crisis depends on its immediate recognition and on the early and continuous administration of iodine. Owing to the proclivity of this reaction to occur early in the course of the disease and before the development of exophthalmos, its abrupt onset may prove confusing. The tendency for crisis to be precipitated by other disturbances, such as acute infections, trauma, miscarriages and the like, may further complicate the picture. Occurring in the debilitated individual, hyperthyroid crisis may present a state of profound prostration rather than that of hyperactivity and excitability which is usually associated with the more intense degree of hyperthyroid stimulation. The abrupt onset of restlessness, excitability and tachycardia in the twenty-four hours succeeding any surgical procedure should lead to a consideration of the possibility that an exophthalmic goiter has been overlooked and if there is any doubt regarding its presence, iodine should be given.

If the administration of iodine is started at the beginning of a crisis, the symptoms are usually controlled in five days. In this time the vomiting ceases and it is apparent that the individual is improving, although several days may be required thereafter for the individual to regain his former strength. If treatment is not given, the crisis may persist for ten days or two weeks. The recognition of the premonitory signs of crisis is important. Spontaneous crisis rarely ends fatally but in exceptional cases such a termination may occur. The administration of iodine does not immediately affect the hyperthyroid symptoms but a period of time is required before its effects become noticeable. H. S. Plummer has suggested the probability that the thyroid secretion already present in the body tissues is not influenced by iodine and that only that produced subsequent to the administration of iodine is influenced. On giving iodine, as the abnormal product present in the body tissues is exhausted it is replaced by a normal product. The improvement in symptoms accompanies this dilution. Since a period of several days may be required before iodine will control the crisis, the patient's vitality may be exhausted in the meantime. Death may occur even three to four days after treatment with iodine is instituted. The recognition of the state of "impending crisis" therefore constitutes a medical emergency and should lead to the immediate administration of adequate quantities of iodine. Lugol's solution should be administered orally in doses of 10 drops diluted with one ounce (30 c.c.) of water each hour for five to ten hours. Persistent vomiting is no contraindication to the use of the oral route. Although the iodine may be retained for only a short time, it is probable that considerable absorption takes place. In addition, iodine is given by rectum by the drip method. A solution of 30 drops in 500 c.c. of saline is used.

For patients who are vomiting, a solution of sodium iodide has been employed intravenously. The dose used is 10 c.c. of a 10 per cent solution. It is doubtful, however, whether this has any advantages over the methods just described.

Amounts of 50 to 100 drops of Lugol's solution, depending on the amount retained, should be given daily in doses of 10 drops each until improvement is apparent; then the dose may be decreased to 40, and then to 30, drops daily.

Because of the abnormal loss of fluid by excessive sweating, vomiting and diarrhea, the administration of adequate amounts of fluid should receive careful attention. The slow injection of physiologic saline solutions intravenously may be used freely if necessary to combat dehydration.

Owing to the high basal metabolic rate and excessive production of heat during the crisis, there is a rapid depletion of the reserve of glycogen. Glucose should be added to the saline given, both intravenously and by rectum. Five hundred cubic centimeters of 10 per cent glucose in a physiologic saline solution may be given once or twice daily. At times patients are first seen at the end of a vomiting crisis when the chief need indicated is the restoration of body fluid.

Moderate to severe degrees of *hepatic damage* are not unusual in cases of exophthalmic goiter of long duration. Jaundice of the sclera may occur and there may be definite jaundice of the skin. More often, however, the only evidence of the presence of hepatic damage is elicited by means of tests of liver function. Moderate to high grades of retention of dye with the bromsulfalein test may be present. Serious hepatic damage is to be suspected in cases in which there is marked debilitation from prolonged hyperthyroidism due to moderate to severe exophthalmic goiter. Prolonged administration of iodine over periods of one to three months together with other appropriate measures including high carbohydrate diet is usually followed by a recovery of the function of the liver as is shown by prompt elimination of dye. Such individuals should not be submitted to operation until all evidence of hepatic damage has disappeared. It is not rare for patients who have severe exophthalmic goiter to experience the development of jaundice following thyroidectomy. Although this also is probably indicative of acute hepatic damage, it is ordinarily not of serious significance and usually does not interfere with prompt postoperative recovery.

The same methods apply in the management of *heart failure* associated with exophthalmic goiter as in the management of adenomatous goiter with hyperthyroidism. However, serious congestive heart failure is much less frequent in cases of exophthalmic goiter than in those of adenomatous goiter with hyperthyroidism. This is principally because persons who have

exophthalmic goiter are in a definitely lower age group than persons who have adenomatous goiter with hyperthyroidism and also because the duration of the hyperthyroidism at the time the patient seeks medical relief is less in cases of exophthalmic goiter than in those of adenomatous goiter with hyperthyroidism. In cases of exophthalmic goiter, the administration of iodine exerts a much greater effect in the control of congestive heart failure than in cases of adenomatous goiter with hyperthyroidism, and in many instances of moderate congestive failure, iodine therapy is sufficient to re-establish circulatory competence without the employment of other agents. Among young individuals who have exophthalmic goiter, serious congestive heart failure almost invariably indicates the presence of independent heart disease, usually mitral stenosis.

The administration of iodine for exophthalmic goiter associated with *diabetes mellitus* is followed by a pronounced decrease in the severity of the diabetes, which parallels the drop in the basal metabolic rate. The management of this complication of exophthalmic goiter is similar to that already described for adenomatous goiter with hyperthyroidism.

Exophthalmic goiter complicating *pregnancy* does not constitute an indication for interruption of pregnancy. Mussey and Plummer found that the use of iodine followed by subtotal thyroidectomy for pregnant women gave a reasonable assurance of subsequent normal gestation and healthy offspring. In those cases in which the administration of iodine is adequate to control the symptoms of hyperthyroidism and in which the patient can be kept under close observation, thyroidectomy may be delayed until after parturition. In cases of adenomatous goiter with hyperthyroidism complicating pregnancy, it is advisable to proceed with thyroidectomy after a few days of administration of iodine, for iodine is not as effective in controlling the hyperthyroidism associated with this condition as it is in controlling the hyperthyroidism associated with exophthalmic goiter.

When exophthalmic goiter is associated with *other diseases* for which operation is indicated, the treatment of the exophthalmic goiter should have priority. This rule should apply regardless of the gravity of the associated disease. Minor procedures as tonsillectomy and dental extractions should be post-

poned until after thyroidectomy. Operations for malignancy should also be delayed as the additional risk of operating in the presence of an exophthalmic goiter more than compensates for the risk of the development of metastasis in the interval. Usually such an operation can be undertaken ten days to two weeks following thyroidectomy. It may be necessary to make an exception to this rule in dealing with very urgent surgical conditions such as acute appendicitis but even then the treatment should be conservative if at all possible, at least until enough iodine has been given to reduce the likelihood of postoperative crisis of exophthalmic goiter. Appendectomy among individuals with severe uncontrolled exophthalmic goiter is associated with a high mortality.

Selection of ideal time for operation.—The selection of the time of operation on an individual who has exophthalmic goiter is a matter of the greatest importance. Serious and unnecessary risk may be entailed by submitting a patient to an operation when unfavorable conditions are present. Such conditions can often be altered by management or, at times, by merely delaying operation until a more favorable time. As a general rule, it may be stated that an operation should not be undertaken when the severity of the hyperthyroidism is increasing. The risk under such circumstances is often so great as to be prohibitive. If there is serious doubt as to the ability of the patient to withstand an operation at a given time, it should be delayed. Remarkable degrees of improvement are often seen in weakened, debilitated individuals following prolonged administration of iodine and adequate general care. It is also true that when the patient has attained a satisfactory state for surgical intervention, operation should not be delayed.

Before a patient who has exophthalmic goiter may be said to be in ideal condition for thyroidectomy, the *following conditions should be fulfilled*:

- (1) The absence of any recent history of serious myocardial insufficiency, gastro-intestinal crisis, or respiratory infection;
- (2) a good intake of food and an increasing weight;
- (3) freedom from severe nervous irritability or stimulation;
- (4) ability to sleep normally;

(5) absence of jaundice or other evidence of hepatic damage;

(6) absence of evidence of myocardial insufficiency, such as edema, moisture in bases of the lungs, coronary pain or dyspnea;

(7) good muscular strength as evidenced by the patient's ability to take a step approximately 15 inches (37.5 cm.) high without assisting himself by using the upper extremities;

(8) recent definite decline in the basal metabolic rate;

(9) continuous administration of liquor iodi compositus in doses of 10 drops three times daily over a period of from seven to fourteen days, and

(10) the patient should be up and around for from four to six hours daily without undue fatigue for four or five days preceding operation.

A given patient may not fulfill all of the conditions and it may be necessary to proceed with thyroidectomy anyway. The risk of the operation, however, will be increased definitely. Hence operation should be delayed until there is no reasonable chance of further improvement with medical management.

Postoperative medical management.—**IODINE.**—We give 30 drops of Lugol's solution a day for two to three weeks postoperatively. We then usually prescribe about 10 drops of Lugol's solution once a day for six weeks followed by 5 drops a day for a year or for an indefinite period of time. Perhaps such large doses are not necessary, but we have never observed any untoward effects. The optimal duration of postoperative treatment with Lugol's solution remains to be determined.

COMPLICATIONS.—The reader is referred back to the discussion of postoperative complications in cases of adenomatous goiter with hyperthyroidism because the complications in this disease are similar to those in cases of exophthalmic goiter. The management of *postoperative myxedema* will be described under the heading "Myxedema."

Recurrences.—Following subtotal thyroidectomy for exophthalmic goiter there is a small percentage of cases in which the disease persists or recurs. In 1930, Pemberton reported 2.9 per cent recurrence among 1683 patients operated on for exophthalmic goiter in the years 1920, 1921 and 1922. Since

among the patients having recurrences there has been a failure of the usual treatment to effect a satisfactory permanent cure, there is naturally an inclination to hesitate before subjecting the patient to further resection of the gland. Among the members of this group the cause which produces exophthalmic goiter appears to be operating with greater persistence than among patients whose exophthalmic goiter was permanently controlled by the initial thyroidectomy and the possibility exists, therefore, that the second resection may be followed by another recurrence. In spite of this possibility it is essential that the hyperthyroidism be controlled. It has been found that the prolonged continuous use of iodine will control the evidences of the disease and will hold the basal metabolic rate well within normal limits in an appreciable percentage of these recurrences. Haines⁴ reported a series of 448 cases of persistent or recurring exophthalmic goiter in which 123 or 25.2 per cent were satisfactorily controlled over prolonged periods by the continuous administration of iodine. The degree of hyperthyroidism and the average basal metabolic rate were much less in these cases at the time of the recurrence than they had been prior to thyroidectomy. In many instances, the administration of iodine was eventually stopped and the patient remained well, evidently on account of a spontaneous remission of the disease. In others, stopping the administration of iodine was followed by a recurrence of symptoms which could again be controlled by resumption of iodine therapy. No ill effects were noted from the prolonged administration of iodine. *Liquor iodi compositus* in doses of 15 to 20 drops daily is given.

In those cases of persistence or recurrence of exophthalmic goiter not controlled by iodine there is usually a greater recurrence of gland tissue than in those satisfactorily controlled. In these cases the indication is for further resection of the gland.

MYXEDEMA

Myxedema appears as a sequela of thyroidectomy or results from thyroiditis. In each case the treatment is the same. It is to be remembered, however, that in some cases of post-operative myxedema it disappears spontaneously. It is unusual these days to see a case of complete or total myxedema with a

basal metabolic rate in the vicinity of -40 per cent. Most of the patients whom we see will have basal metabolic rates in the vicinity of -20 to -30 per cent. Regardless of the etiology or the level of the basal metabolic rate, we use desiccated thyroid gland in practically all of our cases. At the outset we make certain that *cardiovascular disease*, *nephritis*, or other *metabolic disease* is not present. If these diseases are present, the use of desiccated thyroid gland is undertaken with rigid precautions and safeguards. We rely chiefly on the basal metabolic rate as an effective gauge of treatment. Determinations of blood cholesterol are helpful.

We try to elevate the basal metabolic rate to a level in the vicinity of -10 to -5 per cent and then keep it at this level. The amount of desiccated thyroid gland required to do this and the amount required as a maintenance dose will vary. When time is an important factor and when the patient's general physical condition permits, the optimal metabolic level may be reached in two to three weeks. In the case of patients who are not totally myxedematous this may be justifiable. When undertaken, we usually give about 12 grains (0.8 gm.) of desiccated thyroid gland in three or four days, followed by $1\frac{1}{2}$ to 2 grains (0.1 to 0.13 gm.) a day. A basal metabolic rate is obtained every fourth or fifth day. Within three to four weeks we can usually establish the maintenance dose. The latter may range from $\frac{1}{4}$ to 2 grains (0.0167 to 0.13 gm.) a day. In most cases, 1 to $1\frac{1}{2}$ grains (0.065 to 0.1 gm.) a day will suffice. If the patient is totally thyroprivic this same treatment is given but a longer period of observation is imperative and larger daily doses may be desirable. As an alternative to this method, which requires close supervision and considerable experience, and as the procedure of choice in cases of myxedema complicated by some other metabolic or constitutional disease, it is advisable to elevate the rate more slowly. Thus, it may be desirable to start out with $\frac{1}{4}$ or $\frac{1}{2}$ grain (0.0167 or 0.032 gm.) of desiccated thyroid gland a day, allowing several months, if necessary, before establishing the optimal dosage. Except for those postoperative cases in which the condition waxes and wanes spontaneously, myxedema requires indefinite treatment and the patient is to be cautioned to take the desiccated thyroid gland indefinitely. After starting on

treatment, he may notice, within a few days, such symptoms as nausea or headache or generalized aching. The occurrence of these symptoms does not necessarily constitute a contraindication to the use of the desiccated thyroid.

The caloric intake should be generous during the period when the metabolic rate is being elevated. In myxedema following thyroidectomy for exophthalmic goiter, it is well to continue the use of Lugol's solution in small doses, such as 5 minims a day, in addition to the desiccated thyroid gland. In cases of myxedema associated with degenerative diseases such as hypertension or coronary sclerosis, elevation of the basal metabolic rate should be undertaken very slowly and the optimal metabolic level in these cases probably should be not higher than -10 per cent.

There are few, if any, medical problems that lend themselves to more satisfactory treatment than myxedema.

CRETINISM

The successful treatment of cretinism depends in part on making the diagnosis and on starting the treatment early enough. The dosage of desiccated thyroid gland will depend on the age of the child. In infants less than a year of age, Boothby and W. A. Plummer suggest $\frac{1}{16}$ grain (0.004 gm.) as an initial daily dose. The successful management of endemic cretinism is largely prophylactic, that is, to treat the pregnant mother who is hypothyroid. Typical endemic cretinism as seen in parts of Europe does not always respond to the early institution of desiccated thyroid gland.

MALIGNANT DISEASE OF THE THYROID GLAND

The medical management of carcinoma of the thyroid is limited to *diagnosis*. The treatment is primarily a surgical problem and will not be entered into further in this discussion.

THYROIDITIS

The various phases of thyroiditis are classified as follows:

1. Acute thyroiditis.
 - a. Suppurative.
 - b. Nonsuppurative.

2. Chronic thyroiditis.

- a. Chronic simple thyroiditis.
- b. Riedel's struma.
- c. Hashimoto's disease, or lymphadenoid goiter.
- d. Tuberculosis of the thyroid gland.
- e. Syphilis of the thyroid gland.

Acute thyroiditis.—In a study of thyroiditis as observed at The Mayo Clinic, McGee found that in approximately a third of the cases of acute thyroiditis, suppuration occurred. Suppuration occurred more commonly in goiterous thyroid glands than in those that were normal previous to the onset of the inflammation. He also found that in many instances acute thyroiditis occurred during or following acute infections, such as pneumonia, typhoid fever, rheumatic fever, influenza, tonsillitis and infections near the mouth and jaw. In many other instances, however, the disease occurs spontaneously and in the absence of any other infection which could be considered as a possible source. If suppuration occurs, the amount of pus may vary from a small amount to a huge abscess containing many ounces. The abscess usually presents externally but it is said that at times it may present internally with the consequent danger of rupture into the trachea or mediastinum. This outcome, however, appears to be rare. In mild cases of nonsuppurative thyroiditis, the inflammation may subside in a few days although two to three weeks are usually required before all evidences of the process have subsided and in some instances it may persist for several months.

For the *nonsuppurative* type, the treatment is symptomatic. The compound solution of iodine is administered, however, as some degree of hyperthyroidism is usually present. The application of heat would seem likely to encourage resolution, but the patient is usually more comfortable with an ice collar. When suppuration can be demonstrated, prompt drainage is indicated. This is usually followed by rapid relief of symptoms and healing is usually rapid and complete.

There is a wide variation in the degree of acuteness of thyroiditis. Various degrees of lesser severity occur, which can best be described by the term subacute.

Chronic thyroiditis.—Chronic simple thyroiditis is a chronic inflammatory process of low grade characterized patho-

logically by an increase in the connective tissue stroma, infiltration of the gland by lymphocytes, destruction of the parenchyma and diminution in the number of acini. It is characterized clinically by an increase in the size of the gland, usually not to a marked degree, but particularly by an increase in the firmness. There may be moderate tenderness on palpation. There is no general reaction. Of chief importance is its tendency to terminate in a destruction of the functioning thyroid tissue with resulting myxedema.

A very similar, if not identical, type of chronic thyroiditis is often seen associated with exophthalmic goiter. Histologic examination of thyroid gland resected at operation for exophthalmic goiter frequently shows, in addition to the characteristic parenchymatous hypertrophy of exophthalmic goiter, various degrees of round-cell infiltration and connective tissue fibrosis characteristic of a chronic inflammatory process. As the degree of this process increases, the severity of the hyperthyroidism decreases but the tendency toward postoperative myxedema increases, as would be anticipated from a process that destroys parenchymal tissue. No special treatment is indicated.

Riedel's struma also known as ligneous thyroiditis or woody thyroiditis is comparatively rare. It is a clinical entity characterized by a very firm, slowly growing tumor which extends slowly, tending to involve the entire gland. The process tends to involve surrounding structures and tends to produce fixation of the thyroid gland. Pain is a common symptom and dysphagia may be particularly troublesome. Constriction of the trachea with obstructive dyspnea may occur. The outstanding clinical feature is the hardness of the gland. Histologically, the structure of the gland is almost completely replaced by dense fibrous tissue that resembles fibrosarcoma. In a high percentage of cases myxedema develops. Partial resection may be necessary to relieve symptoms that are caused by pressure but operation is usually confined to the performance of a biopsy to distinguish the condition from a malignant lesion.

Hashimoto's thyroiditis, or lymphadenomatous goiter, is a rare condition characterized by a marked lymphocytic infiltration. There is less tendency for pain, dysphagia and dyspnea to occur in cases of Hashimoto's thyroiditis than there

is in Riedel's struma, although these symptoms do occur and may be sufficient to necessitate resection. There is the same tendency for myxedema to develop in this condition as in Riedel's struma.

Tuberculosis of the thyroid gland is rarely associated with clinical tuberculosis of other structures. It produces only a moderate increase in firmness. It is usually associated with hyperthyroidism. Caseation is unusual. It is rarely recognized clinically and resection is usually done because of the diagnosis of exophthalmic goiter. Resection of the thyroid gland is followed by prompt healing and no tendency toward recurrence.

Syphilis of the thyroid gland apparently occurs but there are very few authentic cases on record.

PARASITIC AND FUNGOUS DISEASES OF THE THYROID GLAND

Trypanosoma cruzi and *Taenia echinococcus* are known to invade the thyroid gland, but only infrequently. The reader is referred to special texts on the thyroid gland for accounts of parasitic and fungous diseases of the thyroid gland.

CONGENITAL ANOMALIES OF THE THYROID GLAND

Anomalies of the thyroid gland, as far as they affect function and health, are rare. The thyroid gland may be absent, as in cases of cretinism. Occasionally, aberrant tissue in the tongue or mediastinum will give rise to symptoms of hyperthyroidism or obstruction. These symptoms require surgical intervention.

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PARATHYROID INSUFFICIENCY

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Parathyroid insufficiency is predominantly a disease of women; it rarely affects men. It may follow surgical operations on the thyroid gland, operations directly on the parathyroid glands, or, in rare instances, may occur spontaneously. Following partial thyroidectomy for goiter, hypoparathyroidism occurs in about 0.05 per cent of cases.⁵ It may result from the inadvertent removal of parathyroid glands due to abnormal situation of the glands¹⁰ or possibly from disturbances in circulation or other mechanical interference which may accompany or follow the operation. It is also possible that parathyroid insufficiency may result from inflammatory changes in the parathyroid glands, for rarely instances have been observed of parathyroid insufficiency following late after partial thyroidectomy for microscopically proved thyroiditis. In such cases, myxedema has also occurred.

Parathyroid insufficiency naturally has been reported with greater frequency following total thyroidectomy performed because of heart disease, than following partial thyroidectomy for various types of goiter. Temporary, and frequently severe, parathyroid insufficiency often follows the surgical removal of parathyroid tumors from patients who have hyperparathyroidism. In such case, the parathyroid glands that are not involved in the tumor are probably put at rest by the presence in the body of excessive parathyroid hormone.

Spontaneous parathyroid insufficiency is very rare. The reported cases have been recognized, in many instances, because of accompanying disturbances; for example, cataract, convulsions, symmetrical cerebral calcification and so forth. The insufficiency in such cases is usually severe and usually is of long duration.

SYMPTOMS AND SIGNS

Acute parathyroid insufficiency.—When parathyroid insufficiency follows operations on the thyroid or parathyroid gland, symptoms and signs may occur within twenty-four hours of the operation. The order of onset of symptoms is not consistent and in fact, symptoms may not be mentioned by the patient. Numbness of the face and hands is the most frequently noted symptom. Carpopedal spasm may occur before the numbness is mentioned or noticed. Difficulty in visual accommodation may be an early symptom that may exist for several days before numbness occurs. Laryngeal spasm, a condition which rarely occurs in this condition unless one vocal cord is paralyzed, may be an early and distressing symptom. Because of the seriousness of this symptom, such a condition occurring after thyroidectomy had best be assumed to be due to parathyroid insufficiency and appropriate treatment should be instituted.

Chvostek's sign is almost always positive in cases of acute parathyroid insufficiency. Unfortunately, it is also occasionally positive in an otherwise normal individual, so that its presence is not pathognomonic. Trousseau's sign is slower in becoming positive than is Chvostek's but it is of more significance when positive. However, one must use caution in its interpretation, as I have seen patients with positive Trousseau's signs whose concentration of calcium and phosphorus in the blood was normal and for whom vigorous treatment for parathyroid insufficiency produced no effect on the sign. In this regard, it should be noted that the signs of parathyroid insufficiency have been ably mimicked by some hypersensitive and apprehensive patients.

Chronic parathyroid insufficiency.—In some instances, the symptoms of parathyroid insufficiency are so mild as to be overlooked completely. In such cases, if the condition persists, recognition may be difficult because of the absence of tetany. Fatigue and muscular weakness, gastro-intestinal irritability and trophic disturbances such as marked disturbances in growth of the nails may be encountered. One of the most serious of the disturbances that occur in cases of chronic parathyroid tetany is cataract. Recently, a few cases of symmetrical regions of calcification in the brain have been described in association

with untreated chronic parathyroid insufficiency.⁶ Mental retardation may occur. As in cases of acute tetany, if one vocal cord is paralyzed, frequent and prolonged attacks of laryngeal spasm may occur. During such attacks, respiratory stridor is severe; the vocal cords have been seen to be very close together in one such case.⁷ It is doubtful that such a condition is common. Generalized convulsions are seen occasionally in severe cases of parathyroid insufficiency. Such convulsions are often preceded by typical carpopedal spasm and this may be considered a diagnostic point. Convulsions have not occurred in our cases following control of the insufficiency.

The signs and symptoms of parathyroid insufficiency may occur either in the presence of a low concentration of calcium in the blood and an increase in the inorganic phosphates of the blood or during a period when the concentration of the blood calcium is falling and that of the inorganic phosphates is rising. Ordinarily, in acute cases following thyroidectomy, the concentration of blood calcium will be less than 7 mg. per 100 c.c. and that of the inorganic phosphates greater than 2.5 to 3 mg. per 100 c.c. In chronic cases, blood calcium levels of less than 7 mg. per 100 c.c. are expected. In the same way, inorganic phosphate in the blood occasionally rises to 5 or 6 mg. per 100 c.c. It is important to remember that during a period of falling blood calcium and rising blood phosphorus, the signs and symptoms of the disease may occur even though the actual chemical levels are within the usual normal limits. This situation may exist following the removal of a parathyroid tumor for hyperparathyroidism when the blood calcium is decreasing from its customarily increased level to the normal level.

The level of magnesium in the blood is reduced in cases of parathyroid insufficiency but, at present, the determination of this element is not considered of importance in recognition or treatment of the condition, nor are studies of ionized and unionized calcium essential to the successful diagnosis and management of the disease.

DIFFERENTIAL DIAGNOSIS

Not all patients who present evidences of tetany are suffering from hypoparathyroidism. Tetany associated with *hyperventilation* is usually easily recognized when the patient is seen

in an attack. When the patient's description is obtained and no attack has been witnessed by the physician, hyperventilation tetany may occasionally be misdiagnosed as parathyroid insufficiency. This difficulty should not occur as in the former condition, Trousseau's sign is not usually positive between attacks, or at least unless some degree of hyperventilation exists. The blood calcium and phosphorus are normal. Tetany associated with loss of chlorides due to excessive vomiting is rarely confused with that caused by parathyroid insufficiency. In the case of tetany due to loss of chlorides in vomitus, again, the history is quite different from that associated with parathyroid insufficiency and the results of chemical examinations in the former are entirely different from those in the latter condition. In cases of tetany from excessive vomiting, the concentration of blood chlorides is lowered and that of blood urea is usually elevated; the calcium and phosphorus are normal.

Marked numbness of the extremities that persists after adequate treatment in a case of parathyroid insufficiency should always call to mind the possibility of the existence of *myxedema*, in which condition such a complaint is often heard. A variable degree of myxedema occasionally accompanies parathyroid insufficiency, and of course both conditions must be recognized and be adequately treated to obtain a satisfactory result.

TREATMENT

Calcium.—The treatment of acute parathyroid insufficiency consists essentially in the administration of large doses of calcium. When sufficient urgency exists, calcium may be given intravenously in the form of 10 c.c. of a 10 per cent solution of calcium chloride or of calcium gluconate. The latter, although it contains relatively less calcium than the calcium chloride and must, therefore, be used in larger amounts, has the important advantage of being much less irritating than calcium chloride if small amounts should be deposited outside the vein. Necrosis may follow the inadvertent injection of small quantities of calcium chloride into subcutaneous tissues. In most cases, calcium can be given orally. It may be necessary to give large doses frequently, and when calcium lactate is used, it must be dissolved in very hot water, as relatively

little is absorbed if it is merely mixed with cold water. The lactate given in 2 to 5 gm. doses every fifteen to thirty minutes is usually the most satisfactory therapeutic agent in acute cases. After control has been achieved, maintenance doses vary from 2 to 4 gm. three or four times daily up to 10 gm. four or five times daily.

It has been reported that large doses of calcium salts are not well tolerated by many patients. We have found this to be true only in occasional instances. In some, diarrhea has followed daily doses of 50 gm. or more of calcium lactate, and in some, nausea has occurred. In some cases in which diarrhea has developed, achlorhydria has been found and in these cases and in some of those in which the gastric contents were not examined, the administration of dilute hydrochloric acid has been followed by cessation of diarrhea. In conjunction with calcium some form of vitamin D is essential for adequate treatment. This is true because vitamin D increases the absorption of calcium from the intestine and if vitamin D is not used, many patients will fail to derive from absorption enough calcium to bring the concentration of calcium in the serum to sufficiently high levels to control symptoms of the disease. Boothby⁴ has reported progression of cataracts in a case in which adequate amounts of calcium were given but in which vitamin D was not administered. For practical purposes cod liver oil is very satisfactory, although some patients object to it. They may be given any one of the multitude of preparations that contain adequate amounts of vitamin D. It is possibly true that large doses of vitamin D, such as 25,000 units daily, may enable control of the disease with smaller doses of calcium, but the difference in effect with increasing doses of vitamin D is by no means quantitative and it is desirable to keep the dose of vitamin D low enough to prevent the development of hypercalcemia. Experimentally, very large doses of crystalline vitamin D have been used to control parathyroid insufficiency without the addition of large amounts of calcium, but from a practical standpoint the condition may be readily and cheaply treated by the aforementioned means. In chronic severe cases, reduction of phosphorus in the diet somewhat increases the ease of control, but this, too, is frequently unnecessary.

Dihydrotachysterol (A. T. 10).—In 1934, Holtz, Gissel and Rossman introduced a new drug, dihydrotachysterol (A. T. 10) (Antitetanisches Präparat. Nr. 10) in the treatment of this disease, and subsequently Arnold and Blum, Albright,² MacBryde, and others have described its use in large series of cases. This drug, a fraction of irradiated ergosterol, has the power of increasing the absorption of calcium and of greatly increasing the excretion of phosphorus and acts, therefore, more like the parathyroid hormone than does vitamin D. Used in small doses, such as 2 to 5 c.c. weekly, it makes large doses of calcium unnecessary and offers the easiest and most pleasant method of treatment yet devised. Ordinarily, even with dihydrotachysterol, some calcium should be given and doses of 6 teaspoonfuls of calcium gluconate daily can be taken easily and will make the requirement of dihydrotachysterol (A. T. 10) much less than when no added calcium is taken. Caution must be observed in the use of this drug, as marked elevation of the blood calcium may occur in short periods of time and metastatic calcification and skeletal decalcification have occurred following its experimental use in animals. The individual dose must be ascertained by trial and observation over a period of several weeks or months before it can be continued with safety.

Parathyroid hormone.—The parathyroid hormone had a more important place in treatment in the past than it has since dihydrotachysterol has been made available. At present, the greatest usefulness of the parathyroid hormone is for patients who are acutely ill and are unable to take sufficient doses of calcium orally. Patients who have chronic severe parathyroid insufficiency for whom surgical operations are performed may be treated easily during the first few postoperative days by administration of parathyroid hormone, the usual treatment with calcium and vitamin D or A. T. 10 being resumed after the patient is able to take them orally. For prolonged treatment, even the most severe cases can be controlled readily without use of the hormone.

Guides to treatment.—The most satisfactory guide in treatment is the *chemical examination of the blood*. Ordinarily, if blood calcium levels of 8.5 to 9.5 mg. per 100 c.c. can be maintained, treatment may be considered satisfactory. Cer-

tainly it is not necessary to hold the concentration of calcium in the blood to 10 mg. per 100 c.c. to keep the patient free of symptoms and it is undesirable to hold the calcium at levels higher than 10 mg. per 100 c.c. Recently, Albright¹ has described a criterion for treatment in which the *urinary excretion of calcium* is used as a guide; the dosage of dihydrotachysterol is reduced when large amounts of calcium appear in the urine and is increased when the urine is free of calcium.

Whatever method of treatment is used, control of parathyroid insufficiency can and should be complete and constant. When such control is maintained, the patient, if otherwise well, should maintain normal health and be entirely free from the development of any of the secondary or late disturbances that occur so frequently in chronic cases of long duration. Treatment of the condition should be *constant*, not intermittent, and it is important that, from the start, the patient with chronic parathyroid insufficiency should be aware of the importance of continuous treatment. When convulsions have been present they have entirely ceased after treatment. This has been true even in those cases in which symmetrical cerebral calcification is present, in which the latter condition has, of course, remained unchanged. Thus, it appears certain that the convulsions are not dependent on the cerebral calcification. Convulsions have, in fact, been encountered in many cases in which cerebral calcification could not be demonstrated.

The progress of *cataracts* that result from parathyroid insufficiency is frequently stopped by treatment, although in rare cases progress has continued. Indeed, slight improvement in cataracts has been reported in very rare instances, but it is not certain that the improvement has been great or persistent. Trophic disturbances usually disappear with comparative rapidity. The usual symptoms and such disturbances as laryngeal spasm, difficulty in focusing the eyes and so forth should disappear within a few hours after the institution of adequate treatment. Definite improvement in the mental status has been observed within a few weeks. In many mild cases, it has been possible to discontinue treatment or to reduce it greatly after months or even years and to have no clinical or chemical evidences of recurrence. Patients who have such a condition, however, should be under observation for long periods of time

before being allowed to go free of treatment, as periods of unusual stress such as infection, pregnancy and lactation may be accompanied by recurrence of the disease.

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HYPERPARATHYROIDISM

EDWARD H. RYNEARSON

Shelling wrote a comprehensive survey of the knowledge of the parathyroid glands, and frequent use of his book will be made in this short and informally written account of hyperparathyroidism.

Von Recklinghausen, in 1891, gave the first description of the manifestations of this disease in bone and the disease sometimes bears his name. Askanazy, in 1904, reported the presence of an adenoma in the parathyroid glands of a patient who was suffering from this condition, but the author did not associate the enlargement of the parathyroid glands with the lesions in the bones. In 1907, Erdheim noted this constant relationship but he misinterpreted the findings; he believed that the enlargement of the parathyroid glands is secondary to the condition of the bones, that the latter is the result of their effort to compensate for the decalcification. In 1925, Mandl, trying to prove Erdheim's hypothesis, transplanted four parathyroid glands into the abdominal wall of a man who was suffering from osteitis fibrosa cystica. When these transplants actually seemed to aggravate the patient's symptoms, he explored the thyroid gland and removed the adenoma of the parathyroid gland. The patient's improvement was immediate and the etiology of this disease was established.

Most of the symptoms of hyperparathyroidism relate to disturbances in the metabolism of calcium and phosphorus. The underlying physiologic principles are not completely understood, but present knowledge indicates that the hormone of the parathyroid glands is concerned with regulation of the serum calcium and phosphorus, whereas vitamin D controls the absorption of calcium from the intestine. The parathyroid hormone seemingly causes an increase in the activity of phos-

phatase, which is an enzyme found primarily in the osteoclast cells of bone, in periosteal cells and in the small bowel. The increased activity of this enzyme causes direct removal of calcium from the bones and thus, the serum calcium is elevated. Albright,¹ to whom we are indebted for this knowledge, has emphasized that the serum calcium exists in two forms: the ionized form and that bound with protein. If the ionized form is increased in amount due to disease and if the serum protein is decreased, it can readily be seen that the total value for serum calcium might be considered to be normal, whereas, actually, it is increased. For this reason, determinations of serum protein should be made in borderline cases and if found to be low, an upward correction must be made in the value for calcium. This probably explains why some patients with hyperparathyroidism are reported to have "normal blood calcium."

SYMPTOMS

In considering the symptomatology of this condition, we must emphasize at the outset the *extreme variation* of the symptoms in different stages of the disease and among different patients. Shelling has classified the symptoms under the following headings:

1. *General:*

- (1) Weakness
- (2) Loss of appetite
- (3) Loss of weight
- (4) Muscle and joint pains
- (5) Constipation and abdominal pain
- (6) Bradycardia and cardiac irregularities
- (7) Polydipsia
- (8) Hypochromic anemia

2. *Skeletal:*

- (1) Generalized decalcification
- (2) Cysts and giant-cell tumors
- (3) Fractures
- (4) Lumps
- (5) Skeletal deformities and shortenings
- (6) Epulides

3. *Urinary:*

- (1) Polyuria
- (2) Albuminuria
- (3) Dysuria
- (4) Hematuria
- (5) Milky urine or gravel
- (6) Renal, ureteral, or vesical calculi
- (7) Renal colic
- (8) Diminished renal function
- (9) Nephrocalcinosis

4. *Metastatic:*

- (1) Arterial calcification
- (2) Broncholithiasis and pulmonary calcinosis
- (3) Generalized calcinosis

5. *Metabolic and chemical:*

- (1) Hypercalcemia
- (2) Hypophosphatemia
- (3) Hypercalciuria
- (4) Hyperphosphaturia
- (5) Increase in serum or plasma phosphatase

The "general" symptoms are, of course, the opposite of those seen in cases of *hypoparathyroidism*: muscular weakness, atony and diminished response to stimuli, in contradistinction to the tetany and exaggerated response to stimuli (Chvostek's and Trousseau's signs) as seen in *hypoparathyroidism*.

The skeletal symptoms are those which follow decalcification and cystic changes in the bones. The urinary and metastatic symptoms are the result of the increased transportation and excretion of calcium with abnormal calcium deposition.

DIAGNOSIS

The diagnosis would be easy if each patient had definite symptoms representing each of the types mentioned in the foregoing paragraph. Occasionally, a patient is seen who complains of weakness, atony, and aching in the bones and joints; who has noted a decrease in his height and changes in his bones (and perhaps has had one or more spontaneous fractures);

who has suffered from hematuria and nephrolithiasis; whose roentgenograms reveal typical osteitis fibrosa cystica; whose whole blood chemical studies show a high concentration of serum calcium and phosphatase and a low serum phosphorus; and who has an easily palpable parathyroid tumor. Such cases are not the rule; however, nor is it desirable to wait until this condition develops to make the diagnosis.

Methods of diagnosis.—Albright, Sulkowitch and Bloomberg² have discussed the methods used to diagnose the condition among patients who have a minimal degree of hyperparathyroidism. Twenty-two of their thirty-five patients were not suspected of having the disease when they entered the Massachusetts General Hospital and the diagnosis was made in twelve cases without characteristic bone changes and in eight cases with a very moderate degree of hyperparathyroidism present. They concluded: "The presence or absence of bone disease is not a function of the degree of hyperparathyroidism, some of the severe cases not having it, some of the mild ones having it. Patients with bone disease and high serum phosphatase levels as a rule develop postoperative hypocalcemia; other cases seldom do.

"The term 'border-line' has been applied to mild cases of hyperparathyroidism and refers to the degree of hyperparathyroidism, not to the symptoms. In the diagnosis of such cases, the following points may be important:

"a, The serum protein determination, so that allowance can be made for the bound calcium in interpreting the total calcium value.

"b, A persistently low serum phosphorus level.

"c, The calcium excretion in the urine.

"d, The composition of the stone.

"e, Repeated blood determinations."

SULKOWITCH'S TEST.—We have long needed an inexpensive, simple test to determine the excessive secretion of calcium in the urine to enable us to diagnose hyperparathyroidism. Such a test has been developed by Sulkowitch. He stated: "The Sulkowitch reagent* is a solution containing oxalate

* "Two and five-tenths gm. of oxalic acid, 2.5 gm. of ammonium oxalate and 5 c.c. of glacial acetic acid are dissolved in distilled water and made up to a volume of 150 c.c."

radicals buffered at such a pH that when equal amounts of the reagent are added to urine the calcium will almost immediately come down as a fine white precipitate of calcium oxalate. If there is no precipitate, there is no calcium, and the serum calcium level is probably from 5 to 7.5 mg. per 100 c.c. If there is a fine white cloud, there is a moderate amount of calcium and the level of calcium in the serum is in the satisfactory range. If the precipitate looks like milk, the danger of hypercalcemia is present."

TABLE 1
BLOOD CHEMICAL FINDINGS USEFUL IN DIFFERENTIAL DIAGNOSIS

Disease.	Serum calcium.	Serum inorganic phosphorus.	Serum phosphatase.
Hyperparathyroidism.....	High.	Low.	High.
Osteomalacia.....	Low.	Low.	Normal or high.
Paget's disease.....	Normal.	Normal.	Often increased.
Renal rickets.....	Normal or low.	High.	Increased.
Osteoporosis.....	Normal.	Normal.	Normal.
Bone tumors and cysts....	Normal.	Normal.	Normal.
Multiple myeloma.....	Normal (may be high).		
Metastatic neoplasms.....	Normal or high.	Normal.	Normal.
Xanthomatosis ossium.....	Normal.	Normal.	Usually normal.
Osteogenesis imperfecta....	Normal.	Normal.	Normal.

BLOOD CHEMICAL FINDINGS.—Chemical changes of the blood are usually very helpful and are herewith compared with the findings that are often, but not always, found in association with other diseases of the bones (Table 1). Mention is again made of the importance of checking the *serum protein* in an evaluation of the serum calcium.

ROENTGENOGRAPHIC CHANGES.—Space prevents a complete consideration of the roentgenographic changes associated with this condition. Camp has emphasized the importance of the uniform, miliary, granular osteoporosis and stated that this

mottled atrophy is distinct from the ordinary type seen in cases of osteoporosis and it is found only in cases of hyperparathyroidism. In some regions, decalcification progresses to produce multiple cystic regions of varying size. Cysts may reach a large size and become the site of pathologic fractures. Because of the softness of the bones, bowing kyphosis, narrowing of the pelvis and coxa vara are common.

TREATMENT

Once the diagnosis has been established, *operation* is the treatment of choice. If a tumor is found and is removed, the condition is relieved. In some cases, as is to be expected, a tumor is not found, but hypertrophy or hyperplasia is present and resection is indicated.

This has recently been discussed by Albright, Sulkowitch and Bloomberg.³ One patient reported by them deserves further mention: She was first seen in November, 1933, when she was sixty-two years of age. She had renal calculi and had been passing gravel for seven years. Removal of both lower enlarged parathyroid glands, by Churchill, in December, 1933, did not affect the concentration of calcium or phosphorus in the serum. At the second operation, in February, 1934, a large right upper parathyroid gland was resected, leaving behind about 500 mg. of gland; the left upper gland could not be found. Only transient improvement resulted. In July, 1934, estrogenic hormones were prescribed on the basis that the patient might be suffering from excessive secretion of the pituitary parathyroid principle, to which the estrogens might be antagonistic. No important effect resulted. Roentgen therapy of high voltage was administered to the pituitary, also without effect. In January, 1935, irradiation of the remaining parathyroid gland was attempted but without a definite result. This was repeated in October of the same year. "This treatment gave her a sore throat but the hyperparathyroidism remained the same." Churchill performed a third operation in March, 1936. He found the remainder of the right upper gland to be virtually unchanged and removed most of it, leaving an amount of glandular tissue approximately the size of a normal parathyroid gland. Within two weeks, the concentration of serum calcium was virtually normal. This case illustrates

clearly the surgical difficulties involved and the failure of other methods of treatment.

In many instances in which parathyroid tumors are removed, all the symptoms of hypoparathyroidism develop and these should be treated according to the principles outlined by Haines in this volume. This postoperative complication is only transitory and the metabolism of the body rapidly becomes readjusted.

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DISEASES OF THE ADRENAL GLANDS*

EDWIN J. KEPLER AND EDWARD H. RYNEARSON

Removal of the adrenal glands is followed by a rapid and fatal derangement of fundamental physiologic processes. With the possible exception of the islets of Langerhans, they are therefore, so far as the life of the individual is concerned, the most important endocrine organ of the body. In their evolution they have attained a high degree of perfection: being paired organs, they have a great factor of safety and are relatively invulnerable to trauma; they are rarely incapacitated by disease; and their secretory activity apparently is not easily disturbed either by disorders of metabolism or by pathologic processes elsewhere in the body.

Morphologically and physiologically each adrenal gland should be regarded as two, or possibly three, distinct units. The cortex, in common with the primitive sex gland, is derived from the ventral celomic epithelium. The medulla, on the other hand, in common with the sympathetic nerve cells, takes its origin from the neural crest. As development of the embryo proceeds, the cells that were derived from the neural crest begin to migrate into the growing cortex, where they ultimately form the true medulla. Between the cortex and the medulla there is thought to be a variable layer of tissue which, although prominent in the fetus, involutes shortly after birth. This layer, recently termed by Grollman "the androgenic tissue" histologically is essentially cortical rather than medullary in its architecture. Functionally, it is considered to be a specialized portion of the primitive sex gland, therefore having neither medullary nor true cortical secretory activity.

In the adult person, the adrenal glands are found to be triangular organs situated at the upper pole of each kidney; on

* Some of this material has appeared previously in "The Fundamentals of Internal Medicine" by W. B. Yater, New York, D. Appleton-Century Company, Inc., 1938, pp. 451-509.

the right the gland rests against the vena cava, on the left, it is in contact with the pancreas and splenic artery. The size of the adrenal glands is subject to considerable variation because of the fact that enlargement (chiefly cortical) takes place as the result of various "stresses" such as fever, exposure of the body to cold, certain vitamin deficiency states and other factors.

The cells of the cortical parenchyma are polyhedral in shape and are characterized in part by the presence of numerous lipoid granules. In appearance they appear to be true secretory cells and have certain points in common with the luteal cells of the corpus luteum and the interstitial cells of the testis. The cells of the medulla, in common with those of the chromaffin system in general, are characterized by their staining reaction to chromium salts. They do not have the histologic characteristics of secretory cells; nevertheless, it is generally agreed that they secrete the well-known hormone epinephrine.

In embryologic and histologic features, therefore, the adrenal glands bear a curious and possibly significant resemblance to the pituitary body (see article on the pituitary by Rynearson and Kepler). Both organs may be considered as tripartite structures. Each has its epithelial component comprised of the secretory cells; each has its neural component comprised of cells that histologically should not function, but nevertheless seem to elaborate principles having striking pharmacodynamic properties; finally, each gland has its intermediate zone comprised of cells that are epithelial in character but whose function is on the whole poorly understood and even may be vestigial. The comparison might be carried even further to point out that in both health and disease the behaviors of these two structures have many features in common.

THE ADRENAL CORTEX

Physiology and pathologic physiology.—Although knowledge of the function of the adrenal cortices is admittedly incomplete, certain facts stand out: (1) complete bilateral adrenalectomy is invariably fatal unless the chemical consequences of this procedure are corrected; (2) death results from loss of cortical tissue rather than from loss of medullary tissue; (3) death can be prevented following total adrenalectomy by the administration of sodium chloride to which is added the

sodium salt of certain organic acids, for example, sodium citrate or sodium bicarbonate; (4) survival of adrenalectomized animals is favored by the administration of potent extracts of the adrenal cortex and is facilitated if the intake of potassium is kept low and (5) adrenalectomized animals, when properly treated, can with some difficulty be kept alive, although their capacity to withstand sudden stresses is limited. Such animals appear to be normal. They are able to breed and to reproduce normal offspring even though cortical extract is not administered to them.

Acute adrenal cortical insufficiency is accompanied by chemical and physical changes in the interstitial fluids, blood, and, presumably, the cells. Some of these changes are constant and probably fundamental, whereas others are secondary and variable. Among the changes are: (1) Depletion of the body stores of sodium because of increased urinary excretion of sodium, the total base of the extracellular fluid of the body thereby being reduced. (2) Loss of sodium ions in excess of chloride ions. (3) Decreased urinary excretion of potassium and an increase in the potassium content of the blood. (4) Loss of water from the interstitial spaces and later from the blood. (5) Hemoconcentration and reduction in the total volume of blood. The former is manifested by an increase in the concentration of the plasma proteins and the latter by an increase in the percentage of erythrocytes relative to the plasma. (6) Chemical changes in the blood that are usually indicative of renal insufficiency, but without histopathologic changes in the kidneys. The concentration of the blood non-protein nitrogen, urea, and sulfates increases. (7) Varying degrees of hypoglycemia and disturbances in the mobilization and storage of glycogen. (8) Decreased utilization of oxygen, hypothermia, and lowering of the basal metabolic rate.

The chemical changes enumerated are not apparent early in the course of adrenal insufficiency by chemical analysis of the blood. Eventually most of them can be recognized by studies of the blood chemistry.

Although most workers are now in agreement regarding the actual symptoms and signs (chemical and otherwise) that accompany acute adrenal insufficiency, there are great differences in opinion as to the manner by which these signs and symptoms

are brought about. For clinical purposes the most workable theory can be summarized as follows: In the absence of the adrenal cortical hormone or hormones, the ability of the kidney to excrete sodium (and consequently, chloride), potassium and water is altered in such a way that there is a continuous and excessive excretion of sodium, chloride and water and a diminished excretion of potassium. Consequently, in the interstitial fluids the concentration of sodium and chlorides is decreased and the concentration of potassium is increased. As the effects of these changes become accumulative, the chemistry of the blood itself changes in the manner previously mentioned. When the latter finally occurs, a condition analogous to shock results: the blood pressure decreases; the blood volume decreases; the ability of the kidney to excrete urea and nonprotein nitrogenous products fails and a state of affairs analogous to "extrarenal uremia" finally occurs. This theory is obviously deficient. It offers no explanation for the disturbance in carbohydrate metabolism, which results in hypoglycemia and for certain clinical phenomena that occur with considerable regularity in instances of acute adrenal insufficiency. In spite of its shortcomings, however, it does provide a means of approach to the problems involved in the treatment of acute adrenal insufficiency.

In addition to the potent amorphous extracts already mentioned, crystalline sterones that have varying degrees of potency in the prevention or rectification of acute adrenal cortical insufficiency can be isolated from the adrenal cortex. In chemical structure these substances are closely allied to the purified male and female sex hormones such as androsterone, testosterone, estrone, estriol, progesterone and so forth, and they can be regarded as cortical hormones or as derivatives of a more fundamental cortical hormone. Among the various sterones that have been isolated from the suprarenal cortex, desoxycorticosterone appears to be most active pharmacologically. Desoxycorticosterone acetate is a synthetic product prepared first by Steiger and Reichstein. It appears to be two or three times as active as corticosterone.

As yet hypercortico-adrenalism as it occurs clinically has not been experimentally reproduced by giving large doses of cortical extracts. Administration of cortical extracts consider-

ably in excess of therapeutic dosage produces no profound disturbances in short term experiments. The effects on normal individuals of the continued administration of large doses of the crystalline compounds that have been isolated from the adrenal cortex have not been studied. It is significant that desoxycorticosterone acetate has produced marked generalized edema and an increase in the blood pressure to hypertensive values when given in excess to some patients suffering from Addison's disease. When hypercortico-adrenalism occurs as

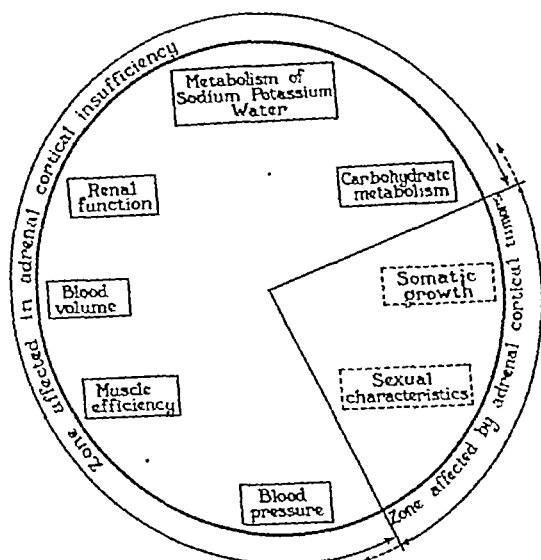


Fig. 130.—Sphere of influence of the adrenal cortex. The zone affected by the adrenal cortical tumors is not sharply demarcated.

the result of disease (for example, cortical tumors), the outstanding disturbances occur in sexual characteristics, usually without demonstrable changes in the metabolism of electrolytes. On the contrary, chronic hypocortico-adrenalism (Addison's disease) usually is not associated with marked disturbances in the sexual characteristics (Fig. 130).

There are still many important unsolved problems concerning cortical adrenal function. Among these are: (1) the number of hormones formed by the cortex and the site and mode of their actions, (2) the relationship of the cortex (or medulla) to

the metabolism of melanin, (3) the relationship of the cortex to carbohydrate metabolism,* (4) the relationship of the cortex to growth, sexual characteristics, lactation, and so forth, and (5) the relationship of cortical activity to the maintenance of normal blood pressure.

Classification of diseases of the adrenal cortex.—Organic disease of the cortex is not common. Functional disorders of the cortex are frequently postulated as an explanation for fatigue states with hypotension, but convincing evidence to support these postulates has not been presented. Two types of endocrinologic disturbance of the cortex are theoretically possible and both occur clinically; they are *hypocortico-adrenalism* and *hypercortico-adrenalism*. In the latter state there is the possibility that disturbed function (the production of an abnormal hormonal chemical molecule) rather than hyperfunction may be the dominant factor. In addition to adrenal cortical disorders that are associated with endocrine symptoms, various pathologic processes occur which often do not produce recognizable disturbances in function. In this connection might be mentioned cysts, benign "adenomas," angiomas, myelolipomas (tumors containing bone marrow in cases of hemolytic jaundice), lipomas, primary malignant tumors (malignant mesotheliomas), miliary tuberculosis, amyloid disease, actinomycosis, and so forth. The malignant tumors either with or without endocrine symptoms sometimes attain large size, tend to invade the renal vein and the vena cava. Secondary growths occur in the lungs, liver, lymphatic glands, and sometimes the brain.

Cortical insufficiency.—Adrenal cortical insufficiency may occur either as an acute or chronic disease and each form has its own peculiar symptoms and problems in diagnosis and treatment. Because of this the two forms should be clearly differentiated:

ETIOLOGY.—*Acute* cortical insufficiency develops either as a result of rapidly destructive lesions of the cortex or following sudden stresses thrown on an individual suffering from chronic adrenal cortical insufficiency (Addison's disease).

* The work of Long and Lukens has shown that experimentally produced diabetes can be ameliorated by removing the adrenals and that corticosterone has diabetogenic properties.

Chronic adrenal insufficiency, or *Addison's disease*, is the end result of slowly progressing destructive lesions of the adrenal cortex. Among such lesions are tuberculosis, atrophy, gummas, and rarely, neoplastic infiltrations. Acute adrenal insufficiency frequently occurs as a terminal event in cases of Addison's disease. Chronic adrenal insufficiency might be termed "compensated adrenal insufficiency."

PATHOLOGY.—*Acute fatal* adrenal insufficiency that is not the result of Addison's disease is usually the sequela of extensive hemorrhages in the adrenals or of thrombosis of the adrenal vessels. Hemorrhages in the adrenal glands followed by acute adrenal insufficiency may occur in newborn infants. The cause of the hemorrhage is not known, although trauma arising from breech deliveries and too vigorous slapping in the lumbar regions to stimulate respiration have been thought to be the etiologic factors in some cases. Hemorrhages may also occur during the course of meningococcemia, scarlet fever, pneumonia, poliomyelitis, diphtheria, and acute pemphigus (Waterhouse-Friderichsen syndrome).

Bilateral adrenal tuberculosis accounts for *chronic adrenal insufficiency* (Addison's disease) in most cases. Active foci of tuberculosis in the lungs, bones, or urinary tract are frequently present. The tuberculous process usually begins in the medulla of the gland or in the deeper layers of the cortex and extends peripherally and ultimately destroys the cortex. There is some evidence to suggest that as the result of chronic low-grade insufficiency, the remaining healthy cortical tissue of the periphery is stimulated to proliferate. This proliferation may take the form of adenomatous tissue that has the capacity to function. Eventually the tuberculosis extends into the newly formed cortical tissue and completely destroys practically all cortical tissue. Symptoms and signs of Addison's disease do not appear until approximately $80\pm$ per cent of the cortex has been destroyed.

In about 10 to 20 per cent of cases, Addison's disease results from bilateral cortical atrophy, the cause of which is unknown. The atrophy begins in the cortex and eventually involves the medulla. Gummas, metastasis, and bilateral tumors only occasionally cause Addison's disease.

SYMPTOMS.—The symptoms of *acute* adrenal insufficiency

are anorexia, vomiting, hiccough, epigastric pain, diarrhea, rapid loss of weight, circulatory collapse, and great prostration, and these occur in rapid sequence. Ultimately, delirium, coma, and death ensue. The terminal symptoms may simulate meningitis or other intracranial lesions. The blood pressure is almost invariably reduced, as is the concentration of the plasma sodium chlorides, and total base. Hypoglycemia, increased plasma potassium, and retention of nitrogenous products in the blood may or may not be present.

The symptoms of *chronic* adrenal insufficiency, or Addison's disease, are, on the other hand, notoriously vague and deceptive in their onset and progress. In some cases fatigue is

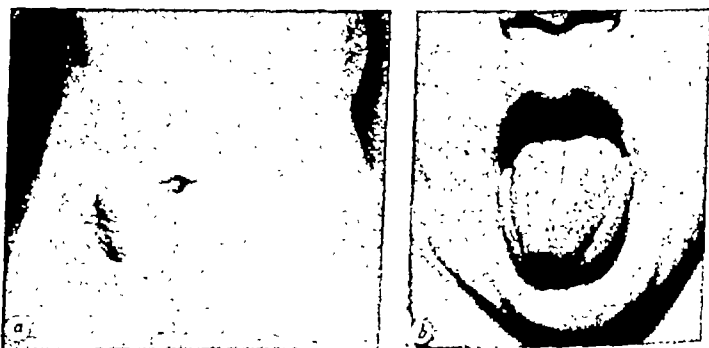


Fig. 131.—a, Pigmentation of scar; b, pigmentation of lips and tongue of a patient with Addison's disease.

the only symptom. Weakness, anorexia, pigmentation of the skin, and loss of weight are among the common earlier symptoms. Attacks of epigastric distress and vomiting, and faintness or fainting attacks are not unusual. An inordinate fondness for salt is sometimes noted. Hypotension of some degree is often present, but blood pressure readings within normal limits are by no means uncommon. The chemical constituents of the blood may be normal in all respects. When patients are not treated, acute cortical insufficiency with its attendant symptoms ultimately makes its appearance.

Pigmentation, although not necessarily a symptom of chronic adrenal insufficiency, usually occurs in cases of Addison's disease and hence occupies an important position in diag-

nosis. It may be generalized or confined to the exposed surfaces (lips, gums, buccal surfaces, scars, pressure points, creases of the palms, and eyelids; Fig. 131). It varies considerably in appearance in different individuals and in the same patient from day to day. Small black freckles may appear on the face, neck and other parts of the body. Often a fine scurf is present on the elbows and behind the ears.

DIAGNOSIS.—*Acute adrenal insufficiency* can usually be recognized in cases of known Addison's disease by: (1) the characteristic change in the clinical picture which accompanies such a "crisis," (2) by studies of the blood chemistry,* and (3) by the rapid response to specific therapy. The diagnosis in cases in which patients are not known to have Addison's disease may be exceedingly difficult, especially if the pigmentation is minimal or absent. The same applies when acute adrenal insufficiency occurs in the newborn infant as the result of hemorrhage into the cortices. The marked prostration, hypotension, and signs of circulatory collapse will give a clue to the diagnostician who thinks of the possibility of metabolic disturbances in cases of patients suffering from obscure acute gastro-intestinal symptoms.

The recognition of compensated adrenal cortical insufficiency (Addison's disease in the stage of chronicity) is not difficult when the classical findings, asthenia, hypotension, and pigmentation, are present. Fatigue states, normal pigmentation in the case of Southern Europeans, arsenical dermatitis, argyria, hemochromatosis, cirrhosis of the liver, retroperitoneal neoplasms, acanthosis nigricans, parasitic melanoderma (vagabonds' disease), chronic peritonitis, pellagra, chloasma, and exophthalmic goiter are among the possibilities to be considered in the differential diagnoses. In less typical instances the diagnosis may be very difficult to make, and special diagnostic procedures may have to be used if the correct diagnosis is to be established. Before proceeding with a discussion of such tests, we must again emphasize the fact that symptoms of adrenal insufficiency do not make their appearance until a large portion ($80\pm$ per cent) of the total cortical tissue has been destroyed. Therefore, theoretically at least, it should

* The characteristic findings (low values for plasma chlorides, plasma sodium and increased blood urea) have been described.

be impossible to recognize any destructive lesion of the cortices until approximately that amount of tissue has been destroyed. Furthermore, practically all the tests that have been devised are in reality not tests for the presence of a destructive pathologic process in the adrenal cortices, but are, rather, only tests for cortical insufficiency. Hence, there is some possibility that at the time the test is made the patient may still have sufficient functioning cortical tissue to interfere with the results of the test. As yet insufficient time has elapsed since the introduction of these tests thoroughly to establish their validity.

Three types of procedures to demonstrate chronic adrenal cortical insufficiency (compensated) have been devised. These three procedures follow:

1. The production of acute adrenal insufficiency by restriction of the intake of sodium chloride has been suggested by Loeb, and by Harrop and associates. The patient should be hospitalized and given a salt-free diet. If the patient has Addison's disease a "crisis" is usually precipitated within one to four days. If no untoward symptoms appear at the end of that time, deprivation of salt can be continued for an additional two days, during which time the patient may be given 6 gm. of potassium citrate. If clinical and chemical signs of acute adrenal insufficiency then do not appear, the physician can be certain that the function of the adrenal cortices is adequate.

2. Estimation of the concentration of sodium and chloride in the urine after the patient has been kept on a standard regimen in which the intake of sodium chloride has been restricted to a low value and in which the intake of potassium has been kept high is a procedure suggested by Cutler, Power, and Wilder. To perform this test the patient is given a diet containing 0.95 gm. chloride ion, 0.59 gm. sodium, and 4.1 gm. potassium. On the first day water is permitted whenever the patient desires it. On the second day water is given to the ratio of 40 c.c. per kilogram of body weight. On the third day 20 c.c. of water per kilogram of body weight is given before 11:00 a.m. Urine is collected from 8:00 a.m. to 12:00 m. on the third day. A concentration of chloride in the urine exceeding 225 mg. per 100 c.c. of urine is indicative of adrenal insufficiency.

3. The effect on the renal excretion of electrolytes following the administration of potent cortical hormone is a procedure formulated by Thorn and his associates.¹²

The first procedure is decidedly hazardous and may terminate fatally. It should never be carried out unless the physician is thoroughly familiar with the early signs and symptoms of early acute adrenal insufficiency and has facilities for treating it promptly. The test should be terminated immediately if adrenal insufficiency ensues. The second test is less hazardous, but it is by no means free of danger and not infrequently has to be terminated on the second day because of acute adrenal insufficiency. It likewise should not be used by the inexperienced. The third procedure is accompanied by no risk, but is not generally applicable because of the necessity of carefully conducted balance studies in a metabolic ward and laboratory. To a lesser extent, the same difficulty applies to the second procedure.

From what has been said, it is evident that as yet there is no ideal test by means of which the diagnosis of Addison's disease can be established. Hence, the physician with limited laboratory facilities may have to rely largely on his clinical judgment and treat some patients in whom the diagnosis is uncertain as if they had Addison's disease until arrangements can be made for a carefully conducted diagnostic study. This course of action, except for the expense involved, can do no great amount of harm and occasionally may save a life.

Most patients suffering from Addison's disease have tuberculosis of the adrenal glands. Many such patients have active tuberculosis elsewhere in the body. Consequently, after the diagnosis of chronic adrenal insufficiency has been made, search should be made for tuberculosis elsewhere in the body. Tuberculosis of the bones, urogenital tract, and lungs not infrequently can be demonstrated. As yet there is no method by means of which the various types of destructive lesions of the cortex can always be distinguished, one from the other. In some instances roentgenograms of the adrenal regions will disclose calcified areas, and in such cases the adrenal lesion most often is tuberculous. If tuberculosis cannot be demonstrated elsewhere in the body, the physician is justified in assuming that the adrenal glands are probably atrophic.

TREATMENT.—*Acute adrenal insufficiency* usually proves to be fatal unless it is recognized promptly and treated vigorously. It constitutes a medical emergency as grave as diabetic coma. To a large measure, successful treatment depends on early recognition of the condition and on the promptness with which treatment is instituted. Anorexia, hiccough, and vomiting are early danger signals in any patient known to have Addison's disease and nearly always indicate an impending crisis. Infections of any sort usually are significant of serious future difficulties, and should be regarded with the greatest respect.

At the onset of symptoms most patients will respond quickly to an intravenous injection of 1 liter of a solution containing 9 gm. of sodium chloride, 5 gm. of sodium citrate, 50 gm. of glucose, and 10 to 20 c.c. of a potent cortical extract. Patients who have been in a state of crisis for an appreciable time will require more vigorous treatment than the foregoing. Ten cubic centimeters of the extract should be administered intravenously hourly and a liter of the salt-citrate-glucose solution at intervals of six hours. There seems to be very little, if any, danger of administering too much extract. Desoxycorticosterone acetate as dispensed at the present time should not be used in the treatment of a crisis, because this substance is administered intramuscularly in sesame oil and has a relatively slow action. If the patient is completely unconscious the outlook is very grave, and if recovery does take place, residual permanent or semipermanent injury to the central nervous system may be the aftermath. After recovery begins, oral administration of the salt and citrate solution should be substituted for the intravenous injections. About 1 liter should be taken daily. Ten to 20 c.c. or more of the extract should be given daily and the amount gradually reduced to the maintenance dosage. If edema appears, the intake of the solution of salt and citrate should be reduced.

There is no unanimity of opinion regarding the maintenance treatment of patients having chronic adrenal insufficiency. Some patients can be maintained in fair health merely by drinking daily 1 liter of a solution containing 10 gm. of sodium chloride and 5 gm. of sodium citrate, especially if the intake of potassium in the diet is restricted. Thompson found that his

patients could be kept well "by administration of an active adrenal cortical extract in an adequate dose (at least 10 c.c. daily and usually much more than this)." The cost of treating Addison's disease solely with cortical extract is prohibitive to most patients. The cost of treatment can be kept within reasonable limits by the combined use of cortical extract and the ingestion of extra salt plus sodium citrate. The amount of cortical extract necessary varies in different individuals and in the same individual under different circumstances and varies with the extract that is used. At The Mayo Clinic some patients have been maintained remarkably well on a regimen consisting of the injection of 5 c.c. of a patent extract two or three times weekly, ingestion of 1 liter of salt and citrate solution daily, and low-potassium diet. Under ordinary circumstances, the less extract used, the more important becomes the use of extra salt and the low-potassium diet. If the patient does not have active tuberculosis he should, when properly treated, feel well and be able to work. Oral administration of adrenal cortical extract should not be relied on. At least three times as much extract is necessary when it is administered in this manner as is necessary when the extract is given parenterally. The cost of such a procedure is prohibitive to most patients; furthermore, there are no extensive series of cases in which patients have been so treated to prove that such patients can be maintained in good health.

Synthetically prepared desoxycorticosterone acetate recently has been made available for general clinical use. This preparation is dispensed in sesame oil and is given intramuscularly in amounts varying from 2.5 to 10 mg. daily. The amount used depends on the intake of sodium chloride and potassium. One milligram of this compound is stated to be the equivalent of 3 c.c. of potent commercial extracts. Opinions are divided regarding the merits of the compound. Thorn and associates,^{9, 11} who have had the most experience with this form of therapy, reported excellent results. However, it is our opinion that for the time being this form of therapy is distinctly and decidedly in the experimental stage and it should be used only by those who have had a large experience with Addison's disease. Our initial experiences at the Clinic with this substance were at first somewhat discouraging. In two cases massive

edema and congestive heart failure occurred, very likely as the result of excessive intake of sodium chloride or excessive dosage of desoxycorticosterone acetate, or both. In two additional cases death occurred suddenly after the patients had returned to their homes. Although the cause of the deaths could not be definitely determined, there is some reason to believe that hypoglycemia was responsible. Recent studies have suggested that there are qualitative differences in the action of various "corticosterones." Desoxycorticosterone has very marked sodium-retaining properties, but seems to be somewhat deficient in maintaining the blood sugar at normal levels. There is also evidence to suggest that it is less effective than some of the other compounds in sustaining the capacity of muscle to perform work. More recently our results following its use have been more gratifying. Loeb reported experiences comparable to ours. Thompson recently stated that "at least another year and probably longer will be required before the status of desoxycorticosterone acetate is precisely determined." We are fully in accord with this opinion.

Thorn^{10, 13} recently reported excellent results in the treatment of Addison's disease by implanting pellets of desoxycorticosterone acetate subcutaneously. These pellets are not available for general use.

Finally, regardless of the type of therapy decided on, certain *adjuncts* to the specific treatment are important: (1) The diet should be high in calories and liberal in vitamins. Food should be taken at regular intervals. (2) The potassium content of the diet should be kept relatively constant at a fairly low value unless desoxycorticosterone acetate is being used. (3) In so far as possible "stresses" of all sorts should be avoided. (4) An effort should be made to avoid the occurrence of infections, and if they occur, intensive treatment with cortical extract should be instituted. (5) Any coexisting tuberculous lesion should be treated.

PROGNOSIS.—In uncomplicated cases, patients do well if treated properly. In many instances the prognosis is determined not only by the Addison's disease, but also by the associated tuberculosis in other organs of the body.

Hyperfunctioning cortical lesions (adrenal virilism, adrenal cortical syndrome, virilisme surrénale).—The dis-

eases caused by these lesions are not only exceedingly rare but are poorly understood. In the discussion that follows only the salient features are presented. For a complete discussion of this topic the reader is referred to an article by one of us (Kepner) which appeared in "Cyclopedia of Medicine." Hyperfunctioning lesions of the adrenal cortex, such as benign or malignant adenoma, carcinoma, or diffuse bilateral cortical hyperplasia, are capable of producing clinical syndromes characterized by profound changes in the sexual organs and characteristics and variable, less specific constitutional symptoms. The etiologic relationship of cortical adrenal tumors to the syndrome has been firmly established. The position of the hyperplastic cortex as a pathogenic focus for the production of endocrine symptoms is much less firmly entrenched. Both types of lesions occur only rarely. Young women are the chief victims. The disease, however, occurs in girls and, occasionally, in boys and men.

BILATERAL CORTICAL HYPERPLASIA.—This condition more often than not occurs in the absence of endocrine symptoms. The endocrine symptoms, when present, are similar to those which occur in association with adrenal cortical tumors. Hyperplasia of the adrenal cortices with endocrine symptoms occurs in association with pseudohermaphroditism, basophilic tumors of the pituitary gland, and occasionally, thymic tumors. There is some reason to believe that in all these conditions the cortical hyperplasia may be responsible for the clinical picture, even though it occurs as a secondary result of a fundamental pathologic lesion.

HYPERFUNCTIONING CORTICAL TUMORS.—*Symptoms.*—The symptoms depend on the age and sex of the individual affected, and on the nature and duration of the cortical tumor. When the syndrome results from a malignant cortical tumor, such factors as the degree of malignancy, duration of the lesion, and the rapidity of its growth, influence materially the clinical picture. These tumors are often encapsulated and are therefore relatively benign. They do, however, have a definite tendency to penetrate the capsule and invade adjacent structures, and they can be extremely malignant. Extension may take place by way of the inferior vena cava, with metastasis to the liver and lungs. These tumors should not be confused with

ordinary carcinomas of the kidney, which unfortunately often are spoken of as "hypernephromas."

Certain variable symptoms occur which are to some extent common to all cases of hyperfunctioning cortical adrenal tumors. These include hypertension, acne, florid complexion, purplish striations of the skin, obesity affecting the face and trunk but sparing the extremities, osteoporosis, latent or frank diabetes, and occasionally, alkalosis with reduced plasma chlorides and potassium. In addition, there may be late symptoms referable to the presence of an expanding lesion in one of the upper quadrants of the abdomen.

Cortical adrenal tumors in boys generally (but not always) result in precocious puberty of the homologous type; that is, puberty is premature but is essentially normal in other respects. In girls these lesions produce precocious puberty of the heterologous type; that is, puberty not only is premature but is more masculine than feminine. The clitoris enlarges, the hair of the body is distributed in masculine fashion, the voice becomes coarse, but the breasts may enlarge and premature menstruation may occur. In children of either sex, dentition may be premature, and the psychic status may correspond to the degree of sexual precocity present.

Cortical tumors in adult males have been known to cause gynecomastia, feminine habitus, disappearance of the beard, loss of libido, and a decrease in the size of the penis and testes. Less than ten cases of this particular condition have been reported to date. The patient in one of these cases presented all of the classical signs and symptoms of pituitary basophilism.

In most cases cortical adrenal tumors occur in young women. Amenorrhea and varying degrees of virilism, such as enlargement of the clitoris, atrophy of the breasts, masculine distribution of the hair, coarse voice, and the like, are the chief characteristics (Figs. 132 and 133).

Pathologic physiology.—At present it is impossible to correlate the known facts regarding cortical insufficiency and the cortical hormone or hormones essential to life with the phenomena which occur as the result of adrenal cortical tumors. There is no doubt that these tumors excrete substances which have powerful hormonal effects, but these same substances may not be secreted by normal glands. The chemical similarity of

the male and female sex hormones and the crystalline cortical sterones is of special significance in this connection.

Diagnosis.—Unfortunately, the syndromes associated with adrenal cortical tumors are by no means pathognomonic. Similar and sometimes identical clinical features occur in connection with the following conditions: (1) basophilic tumors of

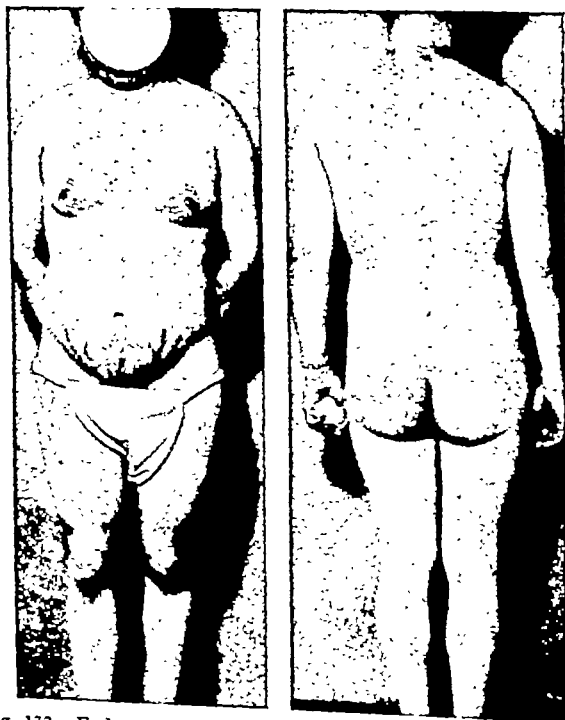


Fig. 132.—End-results of long-standing malignant tumor of adrenal cortex in a woman aged twenty-five years. Note hirsutism, flat breasts, long trunk, short extremities and abdominal striations.

the pituitary gland; (2) various intracranial diseases not directly involving the pituitary body, such as pinealomas, internal hydrocephalus, and inflammatory lesions; (3) hyperfunctioning gonadal tumors, such as arrhenoblastomas and interstitial-cell tumors of the testis, and (4) other diseases already mentioned associated with cortical hyperplasia. In addition, there is a large group of women with varying degrees of hirsutism,

menstrual disturbances and obesity who have no organic lesions of the adrenal glands. These women appear normal in all other respects.

In spite of the obvious difficulties involved, it is important that a conscientious effort be made to establish a diagnosis, since not only do the symptoms of adrenal cortical tumor promptly regress after the tumor has been removed, but death



Fig. 133.—Same case as Fig. 132. Note hirsutism, flat breasts, masculine short hair of the scalp and recession of hair at temples.

from metastasis usually is the result if extirpation of the tumor is not undertaken. Certain procedures may be listed which aid in diagnosis: (1) intravenous urography occasionally will show evidence of a large adrenal tumor, (2) smaller adrenal tumors sometimes can be visualized roentgenographically after air has been injected into the perirenal tissue spaces, (3) in some instances of adrenal cortical carcinoma large amounts of

estrogenic substances can be found in the urine (the results of the usual urinary tests based on the content of gonadotropic hormone of pregnancy will be negative), (4) the urine can be assayed for excess content of androgenic substances, and (5) in some doubtful instances it may be necessary to visualize the adrenal glands by surgical exploration in order to affirm or deny the presence of an adrenal tumor.

It is obvious that, unfortunately, as yet the differentiation of conditions simulating adrenal cortical tumors cannot be reduced to the realm of bedside medicine. Unless the physician has unusual technical facilities at his command, scarcely any course is open to him except to be content with recognition of the fact that the patient's condition belongs in the large group of cases under discussion.

Treatment.—The treatment of adrenal cortical tumors is surgical. After removal of such tumors, failure of the remaining gland (which is often atrophic) can be expected and should be anticipated. Consequently, for one to two days before, and for seven to ten days after operation, such patients should be treated as if they had Addison's disease. This treatment should be continued after the need for it is no longer apparent and then it should be gradually discontinued. If at operation no tumor is found and if the adrenal glands are definitely hyperplastic, unilateral adrenalectomy or partial bilateral resection may be considered. Experience with such surgical procedures has not been sufficiently great to justify unqualified recommendation of them at present.

Prognosis.—Successful resection of a hyperfunctioning adrenal cortical tumor is followed by dramatic improvement. If the tumor has already penetrated its capsule, death from metastatic lesions or from local recurrence can be expected.

THE ADRENAL MEDULLA

Physiology and pathologic physiology.—The adrenal medulla secretes a hormone known as "epinephrine." It can be prepared in crystalline form and its chemical formula has been determined. This substance, although possessed of potent pharmacodynamic properties, seemingly is not necessary to life or well-being, at least not under ordinary conditions. Whether

the secretion of epinephrine is a continuous or intermittent process is still a question. It seems likely that a brisk discharge of epinephrine into the blood stream occurs during periods of emergency or stress.

The effects of epinephrine are for the most part identical with those that occur after stimulation of the sympathetic nervous system. Thus, after an injection of epinephrine, there is a marked rise in arterial blood pressure, acceleration of the heart, and other marked "sympathomimetic" effects of less importance for the present purpose. The concentration of the blood sugar is elevated and the basal metabolic rate is increased.

Diseases of the adrenal medulla.—Diseases of the adrenal medulla occur less frequently than those of the cortex. Although hypofunctioning or hyperfunctioning medullary states are theoretically possible, there is little sound evidence to prove the existence of disease entities that result from medullary insufficiency.

HYPERMEDULLARY ADRENALISM.—Only the briefest consideration of etiology, pathology, symptoms, diagnosis and treatment is possible.

Hypermedullary adrenalism resulting from hyperfunctioning medullary tumors or allied tumors of the chromophil tissue has been established as a definite clinical entity.

The tumors, which are referred to as "paragangliomas," "pheochromocytomas," and so forth, are usually encapsulated, benign, and do not give rise to metastasis. Large amounts of epinephrine have been extracted from them.

The chief *symptoms* are vasomotor attacks, tachycardia and paroxysmal hypertension, nausea, vomiting, and tremor. Glycosuria and elevation of the basal metabolic rate may be present. In rare instances, hypertension may be continuous. Contrary to what might be expected, sweating may occur during the crises. Sudden death, especially from minor surgical procedures, is not uncommon.

The *diagnosis* is often difficult, especially if the patient is not under observation during an attack or if the hypertension is relatively continuous rather than paroxysmal. The repeated occurrence of paroxysms of hypertension justifies a tentative diagnosis of this condition.

Treatment is surgical and, if the tumor can be removed, it results in cure.

MALIGNANT TUMORS OF THE MEDULLA.—Primary malignant tumors of the medulla occur without endocrine symptoms. They usually arise from sympathetic ganglion cells or their derivatives and according to the degree of cellular differentiation present are given such names as sympathogoniomas, sympathoblastomas, neuroblastomas, neurocytomas, gliomas, and so forth. If such a blastoma metastasizes to the liver and produces ascites it is known as the "Pepper type." In the Hutchinson type, metastatic tumors are found in the skull and orbit. There are a few cases on record of bilateral malignant melanocarcinoma of the medulla.

OTHER DISEASES ATTRIBUTED TO ADRENAL GLANDS

The adrenal glands have been held responsible for many other diseases, such as ordinary hypertension, neurocirculatory asthenia, peptic ulcer, recurring hyperthyroidism, diabetes, epilepsy, and various nondescript polyglandular disturbances. The evidence that the adrenal glands play a major part in the production of such conditions is as yet far from convincing.

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ENDOCRINE THERAPY OF CRYPTORCHIDISM, IMPOTENCE AND PROSTATIC OBSTRUCTION

THOMAS L. POOL, EDWARD N. COOK, AND EDWIN J. KEPLER

In the past decade endocrinologists have encroached on a territory that once was considered to be the sole domain of the urologist. A few major clinical achievements and a barrage of literature resulted. In it the endocrinologist occasionally displayed a woeful lack of knowledge regarding the nature of the urologic condition with which he was dealing; with almost equal frequency the urologist disclosed his ignorance of the aims and attainments of endocrine therapy. The bystander, who was not particularly interested in either specialty, literally was caught between the devil and the deep blue sea.

Enough has been said to make it apparent that insufficient factual material is available to justify any attempt to reduce the vast amount of literature into a few working precepts. We have tried, therefore, to limit ourselves to a presentation of some of our clinical impressions and enough physiologic material to make the subject matter intelligible. No attempt has been made to discuss the treatment of hypogenitalism in detail; nor have we felt that it is advisable as yet to review the endocrine therapy of sterility of the male or the so-called "male climacteric."

Physiology.—In contrast to the other members of the endocrine system, which are mostly concerned with the survival of the individual, the function of the gonads is primarily concerned with the survival of the species. The gonads are not essential to the life of the individual and their removal is not followed by changes comparable in magnitude or severity to those that ensue after extirpation of the other organs of internal secretion. They occupy, therefore, a somewhat unique position in the endocrine system and their disorders of function raise clinical problems that are somewhat different in character from

those that are encountered as the result of disease in the other endocrine glands. In addition, they bear a peculiar relationship to the function of the anterior portion of the pituitary body (see article by Ryneerson and Kepler).

More specifically stated, the gonads have a *dual* function: The first, primarily cytogenic, is the harboring of the primitive germ cells and the provision of a suitable medium for their maturation; the second, primarily endocrine, is the formation of hormones which cause the development of, and preserve the maturation of, those organs and characteristics that are necessary for sexual attraction, cohabitation, nurture of the fetus and care of the newborn.

If either the testes or the ovaries are removed before puberty, the secondary sexual organs remain infantile and the secondary sexual characteristics which distinguish the male from the female fail to appear. In addition, union of the epiphyses is delayed so that the extremities become disproportionately long. If the ovaries are removed after puberty, the signs and symptoms of the menopause appear if this has not occurred previously. The effects of castration on men are variable. In some instances impotence and some of the signs of eunuchism make their appearance. However, frequently there is a surprising lack of either subjective or objective departure from normal. It is not particularly unusual to see an adult male patient who has been castrated after normal sexual development has taken place whose libido, potentia and virilism have not been impaired by the loss of his testes. As a rule, the later in life that an individual loses his endogenous supply of testicular hormone the less will be the effect on his somatic and sexual characteristics.

The cytogenic function of the testes is centralized in the seminiferous tubules; the hormonal function, in the interstitial cells of Leydig which are situated in the loose connective tissue between the seminiferous tubules.

The hormone of Leydig's interstitial cells is thought to be a substance which is known as *testosterone*. It has been prepared in the crystalline form and its chemical structure is known. Chemically it is closely allied to other sterols that have hormonal properties, such as progesterone, estriol, desoxycorticosterone and allied substances. As has been mentioned

previously, the development of the secondary sexual organs and characteristics is dependent on the internal secretion of the testis which is presumably testosterone. It is, therefore, responsible for the growth and development of the penis, prostate gland, seminal vesicles, Cowper's glands, masculine bodily habitus and distribution of cutaneous hair, the beard, the masculine type of larynx, and finally, those conduct patterns and psychic attributes such as aggressiveness that are preponderantly masculine traits.

Testosterone is only one of a number of compounds that exhibit these androgenic properties in varying degrees. Among these also should be mentioned *androsterone*. This compound is present in the urine of both men and women. It is considerably less potent than testosterone. A number of androgenic substances have been found also in the urine of patients suffering from adrenal cortical tumors and other conditions that give rise to virilism in women. The germinal cells of the seminiferous tubules have been thought to secrete a hormonal substance known as "inhibin." This principle was so named because of the belief that it had a restraining influence on the stimulation to the interstitial cells by the anterior lobe of the pituitary body. Prostatic growth thereby was inhibited. The benign prostatic hypertrophy which tends to occur in later years of life was thought to be the result of a relative hypersecretion of the interstitial cells. Neither the theory nor the presence of such a germinal hormone has been verified.

Most diseases of the testes do not lead to endocrine disturbances. However, disturbance of the cytogenic function is one of the common effects of any disorder that destroys the functional integrity of the testes, epididymides, seminal vesicles, vasa deferentia or other portions of the masculine genital apparatus. These facts are of fundamental therapeutic importance.

CRYPTORCHIDISM

Descent of the testes usually occurs during the last few weeks of fetal life, although in some cases it takes place spontaneously shortly after birth. One or both testes fail to descend in approximately 0.1 to 0.3 per cent of males of all ages. Undoubtedly this figure would be a little higher if only boys less than the age of ten years were examined, for there is conclusive

proof that in a large percentage of such cases if no anatomic deformity persists, spontaneous descent takes place at puberty.

Cryptorchidism is of great importance because the undescended testis is frequently deficient in spermatogenesis. Of interest is the related fact that there is little or no change in the interstitial cells of such testes. Experimental cryptorchidism produces the same histologic changes and these changes disappear after the testis has been returned to its normal habitat. If the testis remains in an abnormal environment too long, spermatogenesis is impaired permanently and sterility results. Because of this important complication, various operative procedures have been devised to bring the testis into the scrotum. These operations are by no means uniformly successful and they often may be exceedingly difficult to perform. Nonsurgical treatment, therefore, merits serious consideration.

Nonsurgical treatment.—The nonsurgical treatment of cryptorchidism is a recent innovation and almost wholly endocrine in character. The chief substances that have been used are (1) the anterior pituitary-like principle (*A.P.L.*) which occurs in the urine during pregnancy, (2) *extracts* of the *anterior lobe* of the pituitary body itself, (3) *pregnant mares' serum*, and (4) *testosterone propionate*. The success or failure of any of these substances will be determined not only by the potency of the hormonal material, but also to a large extent by anatomic factors such as the shortness of the spermatic vessels of the vas deferens as compared to the length of the passage through which the testes must pass, the disproportion between the size of the testes and the tract, inadequate development of the inguinal canal and scrotum, adhesions of the testes to surrounding structures and abnormalities of the mesorchium.

ANTERIOR PITUITARY-LIKE PRINCIPLE (*A.P.L.*).—As the anterior pituitary-like principle has been used the most, it alone will be considered. It has been given intramuscularly in *doses* varying from 200 to 500 rat units once or twice weekly. This is continued for two to six months, and if further therapy seems indicated, a period of rest is advised because of an apparent loss of sensitivity to the stimulus produced by the hormone. After an interval of three months the sensitivity probably has returned.

The age recommended by different authors at which the drug should be given varies. Many have stated that it should be tried before the age of seven to nine years, and if not successful, operative procedures should be advised. Still others have expressed the belief that because so many undescended testes descend at puberty, this is the best time to administer the drug in order to aid in placing the organ in its normal position. The reason for its earlier use seems to hinge on the question as to whether or not the functional result is the same if surgical replacement becomes necessary and is deferred until puberty is reached.

How successful hormonal therapy of maldescent of the testes has been since its introduction during the past decade is still largely a matter of opinion. A review of the literature discloses great *discrepancies* in the *results* reported by various authors. The work of Thompson and Heckel is perhaps the most conclusive of any of the published reports. They found in the literature an average of 61 per cent of successful results following the administration of "anterior pituitary-like principles" in this type of case. In their own series of cases, descent occurred in only 20 per cent of cases when patients of all ages were considered and in 27 per cent of cases in which the patients were less than sixteen years of age. They were not able to induce descent in any case in which the testis was intra-abdominal or removed from the normal pathway between the inguinal canal and the bottom of the scrotum. They felt that the administration of the substances mentioned above may make it possible to decide which testes will require operative intervention and which will not. They cautioned against continuation of therapy if genital growth became marked and called attention to the many unsolved problems which remain, such as the influence of premature stimulation of the testis on its function later in life, on skeletal growth and on social adjustment.

From this brief résumé, it should be apparent that the *indications* for the use of anterior pituitary-like substance in cases of cryptorchidism have *not been established definitely* to everyone's satisfaction, and that the results of this form of therapy are decidedly uncertain. Furthermore "cures" have been attributed to hormonal therapy when actually the patient never

did have cryptorchidism. The evaluation of therapy is complicated further by the fact that in almost any series of cases reported descent would have occurred spontaneously in some. In spite of the shortcomings of this type of therapy we nevertheless must preserve an open mind for the time being regarding its merits.

TESTOSTERONE PROPIONATE.—There are a number of reports of cases of cryptorchidism in the treatment of which testosterone propionate has been used. There is one serious objection to the use of this substance, namely that it does tend to inhibit spermatogenesis. This inhibition, however, apparently does not seem to be permanent, although as yet it is not known what the ultimate effects of long-continued treatment will be. To us, the use of this substance in this condition appears to be another example of failure to distinguish between the indications for replacement and for stimulating therapy.

Finally, it should be mentioned in passing that the use of almost any of these substances may be of considerable value in the preoperative and postoperative surgical treatment of this condition, because of the growth-stimulating action on the structure with which the surgeon has to work.

IMPOTENCE

One of the common complaints that prompt men of almost any age to seek medical advice is the inability to perform the sexual act. Unfortunately the advice that is given sometimes does not conform to the high standards of quality which is accorded to seemingly more serious matters. Perhaps as the result of the false sense of modesty still current in society as a whole, but more likely because of inadequate information, the medical profession has not given the subject of impotence the careful study that it warrants. Not infrequently the patient is viewed with scorn; more often he is branded as a psychopath. Under such circumstances, the patient can scarcely be blamed for seeking advice from charlatans.

Etiology.—Both *organic* and *functional* causes may lead to impotence. On the whole the former is characterized in part by the entire absence of penile erections whereas the latter is marked by the inability of the patient to obtain an erection at the desired time. Furthermore impotence that is

the result of organic disease is not likely to be a primary complaint as other symptoms are usually more disturbing; whereas, in contrast, impotence that is functional or psychic in origin is usually a dominant if not the sole complaint. Unquestionably the vast majority of patients who seek medical advice because of their sexual weakness have no demonstrable organic disease.

Although coitus is accompanied by intense psychic excitation, fundamentally the act is largely a spinal reflex, the nervous center of which is situated in the lumbar portion of the spinal cord. Consequently any pathologic condition which interferes with the afferent or efferent fibers to or from this center may be the cause of impotence. *Tabes dorsalis*, *multiple sclerosis*, *transverse myelitis* and *lead poisoning* afford examples of impotence of this character. *Diabetes mellitus* and *pernicious anemia* are not infrequent causes of impotence. In these conditions, it is not known whether the disturbance is primarily the result of a neuronitis or whether it is incidental to the disturbance in metabolism. In these two conditions, failure of sexual power may be the initial symptom. Occasionally impotence is the outstanding symptom of *pituitary insufficiency*, for example, that which follows pituitary tumors. In this type of case, other signs of insufficiency of the anterior lobe of the pituitary are usually present (see article by Rynearson and Kepler). Impotence as the result of cachectic disease can be dismissed without comment.

Finally there remain among the *organic* causes for impotence such conditions as castration and as genital hypoplasia which is probably the result of insufficiency of the anterior lobe of the pituitary body in most instances and has been discussed elsewhere. Curiously enough as has been mentioned, castration, when it has been performed after puberty, may not be followed by impotence or any demonstrable ill effects. Once in a great while, however, it may be followed by some of the physical signs that accompany true eunuchism in the full sense of the word.

Diagnosis.—The vast majority of patients who seek advice because of impotence do not have any demonstrable abnormality of either the genital or the endocrine organs. Skillful questioning almost inevitably reveals the fact that this

disability is usually essentially *psychic* in origin. This statement does not imply that the patient is either a hypochondriac or a neurasthenic, or that the psychic factor is necessarily of a major character. Many of these patients have at least the ordinary amount of nervous stability. It generally is not appreciated that the sexual appetite and its normal sequela are disturbed even more easily than the appetite for food. In this respect the history of a patient who was recently under observation at The Mayo Clinic is very illuminating. This patient had been vigorously but unsuccessfully treated for impotence with hormonal preparations. He was happily married, had no unusual worries and appeared to be a stable, well adjusted normal sort of individual. Eventually it was learned that he and his wife had been sleeping in a room which was adjacent to the bedrooms of his three sisters and mother and that the springs of the bed were noisy. Libido and potentia promptly returned without further use of endocrine therapy after he and his wife moved to other quarters.

From what has been said, it should be apparent that impotence per se is in reality a symptom and never a disease. Nevertheless ever since the advent of gonadal stimulating substances and male sex hormones it unfortunately has been regarded more often than not as indicative of testicular insufficiency and treated as such. What have been the results? The facts can scarcely be obtained from the literature. Many of the reports concerning the use of anterior pituitary-like substance (*A.P.L.*), gonadotropic hormone from pregnant mares' serum and testosterone propionate glow with enthusiasm; others are less encouraging and state that no particular benefit has ever been noticed from the use of these substances which could not be explained on the basis of psychotherapy alone.

Treatment.—On the whole the consensus is that anterior pituitary-like substance (*A.P.L.*) is of no value in this condition. The use of the gonadotropic hormone from *pregnant mares' serum* is being tried extensively at present. In our own hands we have not found it to be of any value. As much as 600 units weekly were given to some patients over periods ranging from two to three months without producing any benefit whatsoever. *Testosterone propionate* also has been used very extensively during the past two years. We have seen more than

100 patients suffering from impotence, who have had long, extended courses of therapy with this drug with absolutely no improvement whatsoever. The dosage in each of these cases could be considered adequate and should have been enough to produce benefit if benefit were to be obtained. Our own experience, therefore, forces us to the conclusion that the endocrine therapy of *psychic* impotence is *virtually worthless*.

The endocrine therapy of impotence that is the result of some of the *organic* conditions which have been mentioned previously rests on slightly more solid theoretic footing. *Testosterone propionate*, for example, has been used in cases of diabetes with impotence. We have tried it in a few cases with out much success. In cases of true eunuchism, vigorous replacement therapy with testosterone is unquestionably worth a thorough trial as in a number of instances good results have been obtained. Unfortunately replacement therapy for this condition is frightfully expensive. Likewise in cases of bona fide male hypogenitalism endocrine therapy is indicated if there are reasonable indications that spontaneous development is not likely to occur. Space does not permit a detailed discussion of this very interesting condition. Briefly, however, it may be stated that one of the major problems is the differentiation of hypogenitalism secondary to insufficiency of the anterior lobe of the pituitary from primary hypogonadism. In the former, stimulation therapy* is indicated, and in the latter, replacement therapy is the treatment of choice. In many instances this differentiation unfortunately cannot be made. Both types of therapy have been employed with a certain amount of success. Either type of therapy is likely to fail in cases of long standing.

The indications, therefore, for the use of either testosterone or gonadotropic substances in the treatment of any condition that is characterized by impotence are in our opinion *few in number*. Unlike the ovaries, testes can be inspected and palpated easily. If on examination they seem to be normal and if there are no other objective signs of testicular insufficiency, such as feminine appearance, lack of beard and the other well known stigmata, it is safe to assume that their hormonal func-

*That is, stimulation of testicular function. To this end, anterior pituitary or pituitary-like substances may need to be injected. Thus, replacement pituitary therapy may constitute stimulation testicular therapy.

tion is probably not impaired and that neither stimulating nor replacement therapy is likely to be of any value.

BENIGN PROSTATIC OBSTRUCTION

Since most men who are afflicted with prostatic obstruction also have waning sexual powers, it is natural to think that there may be some connection between these two conditions. Various hypotheses have been introduced in an attempt to explain why some men have adenofibromatous hyperplasia of the prostate gland. It is unnecessary to describe these since so little is known concerning the actual facts.

Lower and his associates reported that approximately 65 per cent of the men treated with desiccated beef testes have received great benefit. The subjective symptoms of these patients were improved greatly and the amount of residual urine was reduced. It was thought that the administration of the testicular substance replaced the inhibin theoretically deficient in these men. Although no decrease in size of the prostate gland could be shown, these patients were said to be relieved by the use of this substance.

Various reports in the literature would lead us to believe that great benefit is derived from the use of *testosterone*. It is, however, questionable whether this benefit is permanent; nor is it likely that the subjective improvement which has been noted is the result of any decrease in the size of the obstructing prostatic gland. It may be that general muscular tone is increased to the degree that a flabby muscular wall is changed to such an extent that urine can be forced past the obstructed vesical neck. If this is true, after use of the male hormone is discontinued, obstruction may recur.

In a recent article Heckel stated clearly that patients having real obstruction of the vesical neck caused by hypertrophy of the prostate gland derived no benefit from the administration of large amounts of testosterone propionate. In his cases the subjective symptoms remained and the amount of residual urine was not reduced. It is also of interest that change could not be found in the tissue removed at the operation that was eventually necessary. This appears to be a very significant observation.

It is too early to expect figures concerning the use of the

gonadotropic principle obtained^c from pregnant mares' serum in the treatment of benign enlargement of the prostate gland to appear in the literature. We can only say now that the theory on which it is based does not appear to be very sound. Perhaps in the future men suffering from obstruction at the vesical neck may be relieved by some form of endocrine therapy. At present, the great majority of such patients will have to submit to operation.

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DISTURBANCES OF FUNCTION OF THE OVARIES

LAWRENCE M. RANDALL

The ovaries are but part of the endocrine system and, in common with the other members of this system, are dependent upon a proper balance of amounts of secretions from the other endocrine glands for normal function. Proper balance of the amounts and timing of secretion of the two known hormones of the ovary are a necessary part of normal function of the ovaries. The ovaries are entirely dependent upon stimulation from the anterior lobe of the pituitary body for initiation of function. The function of the ovaries is limited to the reproductive life of the individual. This function is not necessary to life and probably not of prime importance to the general metabolism of the individual. Ovarian hormones may affect the function or utilization of other hormones, but probably not in an irreplaceable fashion.

In considering the functional disturbances of the ovaries it is necessary to remember that variations in efficacy of stimulation of the ovaries may exist, such as failure of the pituitary body to stimulate the ovary properly or the existence of a lowered rate of metabolism which may be sufficient to embarrass attempts at normal function. The capacity of the ovary to respond to normal stimulation or environment by normal function must vary a great deal in different women. The effect of the endometrium upon ovarian function probably has been underestimated. It is well known, for example, that ovarian function often fails more rapidly after removal of the endometrium at the time of a hysterectomy and that the life of ovarian transplants under such circumstances is less than if some endometrium remained. Too much emphasis has been placed upon the "failure of ovarian function" in the interpretation of endometrial biopsy without realizing that there is a difference in the abilities of endometria to respond to stimulation and to function properly.

In considering this subject, disturbances of function caused by inflammatory disease or neoplasms are excluded. Organic disease of the ovaries is not considered to be the result of an endocrine disturbance, and endocrine therapy has no place in the treatment of such a condition.

It is impossible in an article of this sort to review completely the background of the present day knowledge of the normal and pathologic physiology that must form a basis for the treatment of disturbances of ovarian function. It is obvious that such knowledge is necessary for intelligent diagnosis and treatment. In addition, one should be familiar with the history, physical findings and results of laboratory tests in the case of normal women and in cases of disturbance of the function of the ovaries. Again it is impossible to cover all this ground at this time and stay within the space allowed. I have elected, therefore, to discuss those methods of treatment that are used currently and in a general way to indicate the basis for their employment.

THYROID THERAPY

Basal metabolic rate.—The *normal range* of basal metabolism is stated to be between -10 and $+10$ per cent. Rates above or below these levels may indicate, respectively, hyperthyroidism, or lowered rate of metabolism without myxedema, or myxedema. Perhaps there has been too much tendency to take the basal metabolic rate at its face value as an indication or contraindication for thyroid therapy in cases of disturbance of the physiologic processes of the genital tract, although all patients with evidence of disturbed physiology of the genital tract certainly do not have low basal metabolic rates or need elevation of the basal rate. The internist considers the symptoms of the patient, such as intolerance to cold, dry skin and hair, and fatigability, as clinical evidence of a low basal metabolic rate. If a patient has such symptoms, it may be desirable to elevate the rate; if not, it is likely that the patient will not derive benefit from the administration of desiccated thyroid gland as far as the general symptoms are concerned.

When one comes to the question of the effect of a lowered rate of metabolism on the function of the genitalia, a somewhat different attitude must be adopted. I have tried for a good

many years to forecast the rate of metabolism in women who have amenorrhea, bleeding dysfunction and sterility, by the usual criteria mentioned previously, and on the whole have been unsuccessful. Many of them do not manifest any of the symptoms commonly attributed to lowered rates of metabolism; furthermore, one may be in error to accept as "normal" a rate between the limits mentioned previously in the presence of evidence of abnormal function of the genital tract such as those mentioned.

Therefore, it seems evident that all patients complaining of symptoms resulting from disturbances of function of the genital tract should have a determination of the basal metabolic rate. Preferably this should consist of the *mean of three rates*. If the rate of metabolism is below the accepted normal, in spite of the fact that the patient manifests none of the commonly described symptoms associated with the low rate, it is usually desirable to elevate the rate to approximately —5 per cent. If the basal metabolic rate is within the usually accepted normal, it is probable that the administration of desiccated thyroid gland will not improve the function of the genital tract. However, one occasionally encounters a case in which there are disturbances of the physiologic processes of the genital tract, manifested by symptoms such as atypical bleeding and amenorrhea and so forth, and the basal metabolic rate is found to be within the usual normal range. Some of these patients need elevation of the basal metabolic rate to levels higher than —5 per cent.

ESTROGENIC HORMONE

Naturally occurring* estrogens represent one of the oldest of the modern hormone preparations and enormous quantities have been used. Before using these preparations one should become familiar with the present knowledge of the function of estrin in the body and deduce from that what may rightfully be expected from this form of treatment. For instance, I see no point in treating women who have amenorrhea with estrogenic hormone merely to secure the uterine bleeding which may follow the withdrawal of treatment. No permanent good can come from such treatment. No good evidence exists that

* In contrast to synthetic estrogens.

an infantile or congenitally hypoplastic uterus has ever been permanently benefited by even enormous doses of estrogens given over a long period. Neither is it rational to treat every nervous woman with female sex hormone, nor is it good therapy to say that every woman passing through the menopause should be given "shots." Probably 25 per cent of women in the menopause have sufficient symptoms to justify specific therapy. On the other hand, it is unfair to deprive those in the latter group of the benefits of modern therapy.

Naturally occurring estrogens employed in sufficient doses may be expected to cause proliferation of the endometrium. In the treatment of patients who have *amenorrhea* they are, therefore, useful to cause the endometrium to grow or proliferate. This proliferation may increase the response of the endometrium to the stimulus of the functioning ovary. If the ovary is not capable of function, the proliferation of the endometrium will be maintained only as long as the injection or ingestion of estrogens is continued. It is probably true that an ovary may be stimulated to function more satisfactorily if the endometrium is caused to proliferate and, therefore, to function. It is believed that there is an inter-relationship between the ovary and the endometrium and that function of the ovary is maintained more efficiently if endometrium is present in the body.

Estrogens are of benefit in cases in which *menorrhagia* and/or *metrorrhagia* is associated with *insufficient* or *incomplete proliferation* of the endometrium. Estrogens may cause an increase in the size of the uterus in cases of secondary amenorrhea in which complete atrophy of the uterus has not occurred. Cellular proliferation of the vaginal epithelium is caused by the administration of the estrogens. This fact has led to the successful employment of estrogens in the treatment of *gonorrheal vaginitis* in the young girl and in the treatment of the *senile changes* that occur in the vagina and external genitalia after the menopause. Inhibition of excess production of gonadotropic principle by the anterior lobe of the pituitary body follows the elevation of the concentration of the estrogens in the body. For that reason estrogens are commonly employed in the treatment of menopausal states to relieve those symptoms that occur in the presence of this hyperfunction of the anterior lobe of the pituitary body.

By contrast, stimulation of production of the gonadotropic principle by the anterior lobe of the hypophysis may be aided by the abrupt rise and fall in the concentration of estrogens that occur following the intermittent injection of large doses of estrogens. The duct system of the breast may be stimulated to develop, or function of this tissue may be regulated; hence, the employment of estrogens in the treatment of *chronic cystic mastitis* in some cases.

Estrogen must be present and sufficiently affect the endometrium during the luteal as well as the follicular phase of the menstrual cycle in order to secure the full differentiative or secretory phase of the endometrium. During this part of the menstrual cycle there is probably some synergistic or inter-related action between the estrogen and progesterone. This means that a proper balance between the two must exist. This question of balance is one of the most important considerations in the whole scheme of normal endocrine function.

The *doses* of estrogens necessary to produce a specific effect or to control a symptom vary greatly in different cases. One has only to review the literature on the subject of estrogenic therapy to realize this fact. Each case is a problem in itself and must be properly individualized. The most important consideration is to find that dose which will maintain an *effective concentration* of estrogen in the body. Abruptly decreasing the amount administered will often result in accentuation or recurrence of the symptoms for which the treatment is being given.

SYNTHETIC ESTROGENS (DIETHYLSTILBESTROL)

Recently reports have been appearing concerning the use of this estrogenic substance which bears no chemical similarity to the naturally occurring estrogens. It is now being given a clinical trial in several clinics in this country. It seems to be most effective when given orally and is much more potent than the natural estrogens. Not much is known about the metabolism of this preparation but the suspicion exists that it is not conjugated in the liver and this fact may perhaps remove an important protective mechanism.

In doses of 1 mg., given by mouth at bed time, it has been very effective in treatment of *menopausal symptoms*. It may

produce some nausea and occasional vomiting for the first few days, but these toxic effects usually do not prove serious. Larger doses are more liable to cause these effects although as much as 30 mg. a day has been given.

The general feeling is that this drug is of definite value, but that one should proceed to use it with some caution. We have given it a trial for over nine months at the Clinic, chiefly for treatment of menopausal symptoms, and have not noted any untoward effects except the mild gastric symptoms mentioned previously.

PROGESTERONE

The function of the corpus luteum hormone is primarily that of differentiating or causing a secretory change to develop in an endometrium that previously has been sufficiently proliferated by the action of the estrogens and upon which the estrogens continue to exert an effect. This hormone is necessary for proper function of the pregravid endometrium, for the maintenance of the function of the endometrium during early pregnancy, and probably is necessary for the proper function of the maternal portion of the placenta during the latter part of pregnancy. It acts synergistically with estrogen and has some influence on the metabolism of the estrogens. The metabolism of progesterone apparently must be initiated in the endometrium, although conjugation of progesterone to the form of pregnandiol found in the urine probably takes place in the liver.

Progesterone is used at present in those cases of *atypical bleeding* in which endometrium shows an insufficient progesterone effect and it probably represents substitutional therapy. It is also used in the treatment of *threatened abortion*. The dose is not too well established: Injections of from 1 to 5 mg. given daily or every other day are ordinarily used, although larger amounts have been given.

Perhaps the best results in the treatment of many of the conditions mentioned above will follow the *combined* use of estrogenic hormone and administration of progesterone. The administration of preparations of progesterone to women bleeding from an insufficiently proliferated endometrium has been of little benefit and the administration actually has been followed by an increase in the amount of bleeding. In some cases

of *dysmenorrhea*, progesterone will relieve the uterine cramp or colic. It may be administered intramuscularly during the luteal phase of the menstrual cycle, preceding the flow. The dose, duration of the effect and frequency of injection will have to be determined in each case.

PREGNANT MARES' SERUM

During a certain period in pregnancy in the mare is found a maximal concentration of a principle that has chiefly a follicle-stimulating action. It therefore differs in action from the principle obtained from the placenta and urine of pregnant women. Because of the origin of the material, care must be taken to be certain that the recipient is not sensitive to horse serum or, if so, is desensitized.

At the Clinic, we prefer *intramuscular* to intravenous injection for this reason. The material may be given in doses of 200 Cole-Saunders' units on the seventh, ninth and eleventh days of the menstrual cycle and an additional 400 to 600 units may be administered on the fourteenth day. If no cycle exists, the series of injections may be arbitrarily spaced. Such treatment may be given each month for three courses, or every other month for three courses. If there is no response to these treatments a period of a few months should lapse before repeating the injections for the ovary may become refractory if the administration of this preparation is continued for too long a period of time.

It is rational to use it in this manner in cases of *sterility* in which no other cause can be found aside from failure of follicular development or ovulation, in cases of *bleeding dysfunction* when inadequate proliferation of the endometrium is a factor, and in the *pituitary type of amenorrhea* when one wishes to initiate ovarian function to re-establish the cyclic relationship between the pituitary body and ovary that is necessary for normal function. I see no reason to employ it in the treatment of amenorrhea that is due to primary ovarian failure in which there is evidence of compensatory pituitary hyperfunction. The ovaries in these cases are being subjected to more intensive and efficient stimulation from the excessive production of gonadotropic principle than can be secured by any of the present therapeutic measures.

EXTRACTS OF PREGNANCY URINE WHICH CONTAIN ANTERIOR PITUITARY-LIKE PRINCIPLE OR CHORIONIC PROLAN (A. P. L.)

These preparations have been presumed to cause luteinization of the human ovary and hence have been used extensively in the treatment of *bleeding dysfunction*.

There is no evidence to show that a corpus luteum has been developed in the human ovary as a result of such treatment, although some luteinization of the thecal cells may occur. When preparations of chorionic prolan are injected intramuscularly into a woman whose pituitary body is functioning, the result is probably that of depressing follicular development in the ovary and aiding the process of luteinization. The beneficial effects that have been secured on the bleeding dysfunctions may be explainable because of this action.

It is perhaps true that this form of therapy is most effective in treating bleeding dysfunction in cases in which biopsy of the endometrium reveals a *poorly developed differentiative or secretory phase* of the menstrual cycle. In other words, a poorly functioning corpus luteum already present may be stimulated to better function. When this situation is present, 250 to 1000 rat units of some standard preparation of chorionic prolan may be given every day or every other day for ten days preceding the anticipated menstrual period. If the flow is delayed the medication is stopped. One may administer progesterone in conjunction with the use of the anterior pituitary-like principle. I do not believe that a rational reason exists for the treatment of amenorrhea with this preparation.

ANDROGENS (TESTOSTERONE PROPIONATE)

As yet physicians do not know too much about the pharmacologic action of androgens when they are injected into the human female. Numerous reports have been largely confined to the treatment of bleeding dysfunction. Intramuscular injection of 5 to 200 mg. of testosterone propionate given daily or every other day has controlled the bleeding, although no differentiation or secretory phase could be demonstrated on microscopic examination of the endometrium and marked atrophic changes may occur.

It therefore seems to me that one may well proceed with some caution in using these preparations. If the response is

prompt and a total dose of less than 1000 mg. can be used, they are worth a trial. Certainly to continue to use testosterone propionate for long periods of time or repeated trials of treatment when bleeding recurs after cessation of treatment is not sound therapy.

VITAMINS E AND K

A considerable literature has accumulated concerning the use of *vitamin E*, in the form of wheat germ oil, particularly for the treatment of *threatened* and *habitual abortion*. Definite beneficial effects have been noted. Perhaps some of the failures have been due to the fact that the preparations of wheat germ oil may vary in potency or may lose their potency after a relatively short time. A synthetic vitamin E has been discovered and will be given clinical trial. Perhaps after this has occurred one can be more specific about the value of this substance. At present sufficient data have been collected to warrant the continued use of the present day vitamin E preparations.

Vitamin K has not proved of value in the treatment of menometrorrhagia. It may prove of benefit in the treatment of *hemorrhagic disease of the newborn*. I believe that it should be given a thorough trial in the treatment of this serious condition as soon as the diagnosis can be made. Experience may also prove that this vitamin will be of value in preventing some instances of *postpartum bleeding*. Perhaps one will be justified in administering it as a prophylactic measure to both mother and infant.

NUTRITION

Abnormalities of menstrual function are frequently associated with altered nutritional states. No doubt many instances of dysfunctions of the ovary in adolescent females seen today could be traced to improper nutrition during the early part of the growth period of the individual. Amenorrhea is not uncommonly seen among women who are markedly underweight as a result of a strenuous reduction diet, or in association with a state of anorexia nervosa. An adequate diet and vitamin supplements which secure a return to normal weight may be accompanied by resumption of a normal menstrual function. In some cases a glandular dysfunction is diagnosed

on the basis of overweight; in some of these cases typical symptoms of glandular dysfunction may be associated with the obesity and such a diagnosis may be indicated. However, I have seen a number of cases of obesity in which a rigid reduction diet with supplements* secured not only a normal weight but a normal menstrual function as well. For the obese or underweight woman other forms of therapy are often needed, but the state of nutrition should not be overlooked when considering the causes and treatment of menstrual disturbances.

ROENTGEN THERAPY

Low voltage or the so-called stimulating doses of roentgen rays may be used in the treatment of menstrual dysfunctions in young women due to certain causes.

This form of therapy has been particularly useful in treating *amenorrhea* in cases in which the patients are women less than thirty years of age when examination of the urine reveals subnormal amounts of gonadotropic principle and estrogen. In such cases the amenorrhea is presumed to be the result of the failure of the anterior lobe of the pituitary body to secrete normal amounts of gonadotropic principle. In this type of case the ovaries, as well as the pituitary body, are treated. When primary ovarian failure exists in the presence of excessive amounts of gonadotropic principle in the urine, which indicates hyperfunction of the anterior lobe of the pituitary body (menopause), this therapy is not indicated in the treatment of amenorrhea. In general, women *past the age of thirty-three years* should *not* be given this form of treatment.

The *technic* which we have employed at the Clinic for a number of years is as follows: 200 kilovolts, 15 to 20 milliamperes with 0.75 mm. of copper and 1 mm. of aluminum as a filter given at a distance of 50 cm. for a period of five minutes. This represents a sixth of an erythema dose to the skin. One field over each temporal region, centered over the pituitary body, and one field over the front of the abdomen, centered over each ovary, are treated. If the treatment is to be effective, menstruation will usually occur in either one or five weeks after the treatment. Such treatment may be repeated in two to

* Supplementary substances consist of calcium, vitamin B complex, vitamins A and D, and iron.

three months, if necessary. We have treated some patients as many as five times and the treatment produced normal menstrual periods for several months.

RADIUM

Radium may be used in the treatment of *atypical bleeding* from the uterus when more conservative treatment has failed. It should be applied in the uterine cavity following a preliminary dilatation and curettage and microscopic examination of the endometrium that is removed.

In general, the *dose* varies with the age of the patient: Women less than twenty should receive 150 to 200 mc. hours; those from twenty to thirty years, 200 to 250 mc. hours; and those from thirty to forty years, 250 to 500 mc. hours. Patients more than forty years of age may be given a submenopausal dose, but after this age a full menopausal dose of 1200 to 1500 mc. hours often is administered to patients with atypical uterine bleeding after a microscopic examination of the endometrium has excluded the presence of cancer.

No woman should receive an application of radium to the uterine cavity *without a preliminary microscopic examination of the endometrium*, made after a *thorough curettage* has been done. After a submenopausal dose of radium has been given, amenorrhea may occur for several months and may be succeeded by the establishment of a reasonably normal menstrual cycle and flow. Numerous instances of pregnancy after such therapy has been administered are on record.

PELVIC HEATING

I doubt if much attention has been given to the employment of this form of treatment for physiologic disturbances of the genital tract of women. Because the blood supply has a good deal to do with normal function of any tissue, it has always seemed logical to me that local heating of the pelvis should have a place in the treatment of dysfunction of the genital tract in certain cases. In the first place there may exist some residual pelvic inflammatory disease and with the absorption of exudates and the freeing of adhesions the blood supply may be so improved that normal function is favored. In such cases either atypical bleeding or amenorrhea has been encountered. In

cases in which amenorrhea is associated with hypoplasia or atrophy of the uterus it seems reasonable to expect that the hyperemia resulting from local heating of the pelvis would favor growth if the proper hormonal stimulus is present to stimulate the uterus.

The heating may be secured by such means as *diathermy*, using the metal belt around the pelvis, but preferably in conjunction with a vaginal electrode, or by means of the *Elliott apparatus*.

I doubt if this form of treatment alone will avail a great deal but, used in conjunction with other forms of treatment, it may be of considerable assistance in securing a good result.

MOCCASIN VENOM

Some time ago the use of a 1:3000 solution of moccasin venom was suggested more or less empirically for the treatment of bleeding menstrual dysfunctions. This seemed logical on the basis that the venom had been shown to reduce capillary permeability in other types of hemorrhagic conditions.

Some of the recent work on the actual mechanism that produces menstruation has indicated that the bleeding is initiated by the breakdown of the spiral arterioles in the endometrium. It is known that bleeding of cyclic nature can occur from any of the various types of endometrium. This forces one to conclude that the stage of the development of the endometrium during the menstrual cycle is not the only determining factor in whether or not bleeding occurs. This is further borne out by the fact that after controlling atypical uterine bleeding by moccasin venom no change in the phase of the endometrium can be detected on microscopic examination.

It is probably a better therapeutic approach first to attempt to secure a normal differentiated endometrium in cases of atypical uterine bleeding, but in some instances this seems impossible. In such cases moccasin venom may be given a trial.

The *technic of administration* is as follows: the first dose of 0.3 c.c. is given subcutaneously; three days later 0.4 c.c., and then three days after that 0.5 c.c. is given. Following this dose there is usually a local reaction consisting of a swell-

ing of the extremity and a rather marked region of ecchymosis develops around the site of the injection. There is no general reaction and there usually is little pain. The swelling may be treated by the application of ice packs. The next dose, given after four days, should be 0.05 c.c., and if no reaction occurs, 0.1 c.c. is given after three days. The dose is gradually increased every third day by 0.2 c.c. until a full cubic centimeter is given. The venom is given in this dose twice a week for about three weeks, followed by the administration of 1.0 c.c. each week. As soon as the patient becomes immune to the material there is no pain on injection and no after-effects. At about this time the atypical uterine bleeding should become improved and in the cases that we have observed this has occurred about the second period after the injections have been commenced. When a second reaction occurs after the dose of 0.05 c.c., the same dose is repeated in four days, after which the usual procedure is followed.

EMPLOYMENT OF SURGICAL MEASURES

Hysterectomy.—With the present methods of medical management this radical treatment should be necessary very rarely in the treatment of atypical uterine bleeding in the *young* woman. For the *older* group of women, who are between thirty and forty years of age and in whom cancer has been excluded but in whom the *menorrhagia* or *metrorrhagia* cannot be controlled satisfactorily by medical treatment, I believe one should seriously consider hysterectomy.

Experience has shown that there may be a recurrence of atypical bleeding in the younger women sooner or later, even after large intra-uterine doses of radium have been given or after the administration of a dose of roentgen rays that is considered to be sufficient to inhibit function of the ovaries permanently. The ovaries have a definite tendency to attempt to function from the drive of pituitary stimulation. Furthermore, in order to have a reasonable expectancy of successful treatment by roentgen therapy one frequently must precipitate an often undesirable artificial menopause, whereas by hysterectomy, conserving the ovaries, this is avoided. This philosophy that favors hysterectomy is based on the fact that persistent atypical uterine bleeding in women in the latter part of the

reproductive period is often unsatisfactorily treated medically. Assuming that operative mortality can be 1 per cent or less and that the morbidity and mortality of these women subsequently is probably more than that, hysterectomy seems reasonable as a treatment measure.

In cases in which the patients are more than forty years of age or are definitely in the menopause, I think endocrine therapy has no place in the treatment of bleeding dysfunction.

DILATATION AND CURETTAGE AND ENDOMETRIAL BIOPSY

I stated before that radium should never be applied in the uterus without a preliminary dilatation and curettage and microscopic examination of the endometrium. One may go farther and say that amenorrhea or atypical uterine bleeding should not be treated until a microscopic examination of the endometrium is made. Nothing is gained by giving luteal hormone to a patient who has such bleeding associated with a poorly proliferated endometrium, nor is estrogenic hormone alone of any use in a case in which the endometrium already is overstimulated with estrin but shows a poorly developed secretory phase.

Endometrial biopsy can easily be done in the office without anesthesia and with a minimal amount of discomfort. If facilities do not exist for this procedure, dilatation and curettage under intravenous anesthesia is a simple procedure.

Exceptions may be made in the case of young girls, but no exception should be made in the case of a woman in the latter part of menstrual life. Thorough curettage of the uterus is often a valuable method of treatment for patients who have menorrhagia or metrorrhagia. The removal of the abnormal endometrium alone may at times be sufficient treatment. In other cases this removal, followed by appropriate medical treatment, may often control the abnormal bleeding satisfactorily.

THE ADVISABILITY OF RESTORING NORMAL RHYTHM IN PATIENTS WHO HAVE AURICULAR FIBRILLATION

HARRY L. SMITH.

When attempting to restore normal cardiac rhythm in patients who have auricular fibrillation, it is well to keep in mind the fact that the prognosis for these patients depends upon underlying pathologic processes and not upon the auricular fibrillation. It is a well-known fact that patients who have mild cardiac disease and chronic auricular fibrillation may live for years and follow a rather active normal life.

However, there is evidence that hearts in which there is normal rhythm are more efficient than those in which there is auricular fibrillation, provided other factors are equal. There still exists a variance of opinion among physicians regarding the advisability of attempting to restore normal rhythm by the administration of quinidine in instances of auricular fibrillation.

In a series of forty-one cases of auricular fibrillation in which the patients were treated with quinidine and strychnine, normal cardiac rhythm was re-established for thirty-three patients, or 80.4 per cent. The ages of these forty-one patients varied from twenty to seventy-six years.

Etiologic considerations.—In the aforementioned series, the auricular fibrillation was classified as *idiopathic* in four instances; that is, it was the only evidence of organic heart disease. In five cases the fibrillation was the result of *hyperthyroidism*; two of the patients also had hypertension and coronary sclerosis. There were six cases in which the auricular fibrillation was associated with *hypertension* and *coronary sclerosis*. In twelve cases it was the result of *rheumatic heart disease*, and in fourteen cases it was the result of *coronary sclerosis*.

State of compensation.—The compensation was good in twenty-five cases, but a varying degree of congestive heart

failure was present in the remaining sixteen cases. In twelve of the sixteen cases the heart failure was mild and in four cases it was severe.

Duration of auricular fibrillation.—In most cases it is difficult to determine the *time of onset* of auricular fibrillation. In the series under consideration, as far as could be determined, the time that had elapsed between the onset of auricular fibrillation and the institution of treatment was one week in two cases, six weeks in four cases, from two to three months in seven cases, four months in four cases, six months in two cases, seven months in one case, ten months in one case, one year in seven cases, two years in five cases, three years in three cases, five years in two cases, seven years in one case, eight years in one case and ten years in one case.

While these figures are not strictly accurate, I am reasonably certain that auricular fibrillation had been present for at least the indicated time.

Amount of quinidine administered.—In most cases 5 grains (0.3 gm.) of quinidine was administered every three hours and $\frac{1}{40}$ or $\frac{1}{30}$ grain (0.0016 or 0.0022 gm.) of strychnine sulfate was administered three times a day, depending on the weight of the patient. The total amount of quinidine that was administered before normal cardiac rhythm was established was 10 grains (0.65 gm.) in one case, 15 grains (1 gm.) in three cases, 20 grains (1.3 gm.) in six cases, 30 grains (2 gm.) in eight cases, 40 grains (2.6 gm.) in seven cases, 50 grains (3.2 gm.) in three cases, 60 grains (4 gm.) in four cases, 90 grains (6 gm.) in one case, 100 grains (6.6 gm.) in two cases, 120 grains (8 gm.) in one case, 130 grains (8.65 gm.) in one case, 165 grains (11 gm.) in one case, 190 grains (12.6 gm.) in one case, 200 grains (13.2 gm.) in one case and 2620 grains (175 gm.) in one case.

In thirty-one, or 75.6 per cent, of the cases the amount of quinidine required to restore normal cardiac rhythm was 60 grains (4 gm.) or less. In eight cases from 90 to 200 grains (6 to 13.2 gm.), or an average of 124 grains (8.24 gm.), was required. As previously stated, 2620 grains (175 gm.) was required in one case. The patient was a man who had rheumatic endocarditis and mitral stenosis. His left leg had been amputated because of acute occlusion of the femoral artery. Auricu-

lar fibrillation had been present continuously for seven years before the patient came to The Mayo Clinic. A total of 135 grains (9 gm.) of quinidine was administered in five days. During this period $\frac{1}{40}$ grain (0.0016 gm.) of strychnine sulfate was administered three times a day. Auricular flutter developed on the fifth day and persisted for sixty-six days. The patient took a total of 2620 grains (175 gm.) of quinidine, or an average of about 40 grains (2.6 gm.) a day, before normal cardiac rhythm was established. The dose of quinidine was then reduced to 5 grains (0.3 gm.), which was administered four times a day for a few days and then was administered three times a day. When the patient was examined one year after his dismissal it was found that the cardiac rhythm was still normal.

Onset of auricular flutter.—In cases of auricular fibrillation it is relatively common for auricular flutter to develop while quinidine is being administered. In a review of the literature Warren found that auricular flutter developed in thirty-nine, or 14.8 per cent, of 263 cases of auricular fibrillation in which quinidine was administered. Once auricular flutter develops, it may continue permanently, it may revert to auricular fibrillation, or normal cardiac rhythm may return.

Auricular flutter developed in four, or 9.7 per cent, of the cases in this series. In one case it developed after the administration of 20 grains (1.3 gm.) of quinidine; in two cases it developed after the administration of 65 grains (4.3 gm.) and in one case it developed after the administration of 135 grains (9 gm.). In one case the flutter lasted for sixty-six days before normal cardiac rhythm returned; in one case the flutter persisted permanently, and in two cases it reverted to auricular fibrillation.

ILL EFFECTS OF QUINIDINE

Toxic effects.—*Nausea, vomiting, diarrhea, weakness and palpitation* developed in four, or 9.7 per cent, of the cases in this series. In two of these cases the symptoms were mild but in two cases they were fairly severe. In the four cases the symptoms of toxemia developed after the administration of 40 grains (2.6 gm.), 45 grains (3 gm.), 65 grains (4.3 gm.) and 210 grains (14 gm.), respectively. In all these cases the ad-

ministration of quinidine was discontinued at the onset of symptoms of toxemia.

Embolism.—Cerebral embolism did not occur while the patients were being treated or while they were under observation at the Clinic. In three cases there was a *history* of cerebral embolism and hemiplegia. One of these patients had had a stroke two years before treatment was instituted and rather complete hemiplegia was still present when the patient came to the Clinic. Another patient had had a stroke three months prior to the beginning of treatment. In the third case the treatment was started immediately after the development of hemiplegia; in this case normal cardiac rhythm was established and maintained by administration of a minimal amount of quinidine.

Peripheral arterial occlusion.—In no case did arterial occlusion occur while the patient was being treated. In three cases arterial occlusion had occurred *before the treatment was begun*. In one of these cases occlusion of the femoral artery had necessitated amputation of the right leg three years before the patient came to the Clinic. Another patient had had acute occlusion of the femoral artery which had necessitated amputation of the left leg below the knee. In the third case, in which auricular fibrillation was associated with mitral stenosis, the treatment was started immediately after the occurrence of acute occlusion of both popliteal arteries; in this case, normal cardiac rhythm was established and maintained.

Sudden death.—Sudden death occurred in three cases. One of these patients was a woman aged forty-five who had chronic rheumatic endocarditis, myocardial insufficiency and a considerable degree of cardiac enlargement.

The second patient who died suddenly was a man aged fifty-seven who had an adenomatous goiter, hyperthyroidism and auricular fibrillation. He probably had had hypertension previously. Auricular fibrillation had been present continuously for six months before he came to the Clinic.

The third patient who died suddenly was a man aged fifty-three who had hypertension, coronary sclerosis, auricular fibrillation and cardiac hypertrophy. Auricular fibrillation probably had been present for several weeks before the patient

came to the Clinic. He had a moderate degree of congestive heart failure and was admitted to the hospital.

ANALYSIS OF RESULTS

In the past it has been believed that the production of embolism by the detachment of a clot was the real danger and that it was the cause of death in cases in which quinidine had been administered. In this series of forty-one cases, embolism did not occur while the patients were being treated or while they were under observation at the Clinic.

In the past, the possibility of embolism has been the chief objection to the administration of quinidine. Some investigators have observed that the occurrence of embolism is not any more common in cases of heart disease in which quinidine is administered than it is in cases in which quinidine is not administered. I feel certain that this objection has been greatly overemphasized.

TYPE OF PATIENT WHO SHOULD RECEIVE QUINIDINE

It seems to me that quinidine is especially indicated when the patients are *young* persons who have *idiopathic* auricular fibrillation but who *do not have* any other evidence of heart disease. The next group of patients who should receive quinidine are those who have a *minimal amount* of heart disease and who have had auricular fibrillation only a *short* time. Quinidine should also be administered in cases in which auricular fibrillation is caused by *hyperthyroidism*, is *not* associated with any significant evidence of organic heart disease, and *continues* several weeks after thyroidectomy has been performed. Patients for whom the least amount of the drug is required to establish normal cardiac rhythm are those who are about fifty-five or sixty years of age, have a moderate degree of coronary sclerosis, have a good degree of cardiac compensation and have had auricular fibrillation for a relatively short time. In most instances of this type, only a few doses of quinidine are required to restore normal rhythm and in a large percentage of cases normal rhythm can be maintained for many years.

I believe that patients for whom it is *most dangerous* to administer quinidine are those who are *elderly*, who have rather serious *hypertension* and *coronary sclerosis*, with rather marked

cardiac enlargement, and who have had auricular fibrillation for a *long time*.

It probably is not advisable to attempt to establish normal rhythm with quinidine in any instance of severe *congestive heart failure*. There is a group, however, which I believe is an exception to this statement. In this group the patients have considerable heart disease with varying amounts of heart failure, and emboli continue to form. These emboli may be cerebral, pulmonary or may occur in the peripheral vessels. In this group of patients I believe that the physician is justified in taking a greater risk to establish normal rhythm. The patients are less likely to have emboli if normal rhythm can be restored. I believe that the possibility of clots being detached as emboli when the auricles resume their normal rhythm has been greatly overemphasized.

I believe that the greatest danger in administering quinidine is the possible occurrence of sudden death. This danger has to be considered seriously and weighed against the benefit that the patient receives when normal cardiac rhythm is re-established. In well selected cases, I believe that there is ample proof that this danger is slight. Patients whose normal rhythm is restored and maintained undoubtedly are greatly benefited by the administration of quinidine.

THE SIGNIFICANCE OF HYPERREACTION OF THE USUALLY NORMAL BLOOD PRESSURE

EDGAR A. HINES, JR.

The systemic blood pressure is variable and it reacts to various forms of external and internal stimulation. Fluctuation of blood pressure occurs both in persons with normal blood pressure and in those with hypertension. Such fluctuations of blood pressure have contributed to the difficulty of determining "normal" blood pressure, since in determining the normal figure one does not know whether to use, for example, the "normal" figure of 120 mm. of mercury, which is the systolic blood pressure reading one day, or the figure, apparently equally normal, of 140 mm., which may be obtained the next day. Some of the difficulty encountered in determining whether an individual has a "normal" blood pressure can be eliminated by considering the range of blood pressure response of an individual in addition to the level of the blood pressure at any given moment. One method of determining the range of blood pressure is to make *consecutive* readings of blood pressure at hourly or half-hourly intervals for twenty-four to forty-eight hours during periods in which the patient is active and during periods of rest. This entails considerable time and cannot be carried out without the close co-operation of the patient. Another method of determining the range of variability of the blood pressure is by the use of a test which measures the reaction of the blood pressure to a *standard stimulus* after a *basal level* of blood pressure has been established. The cold pressor test is a satisfactory test for determining the reactivity of the blood pressure.

TECHNIC OF THE COLD PRESSOR TEST

The subject is allowed to rest in a supine position in a quiet room for twenty to sixty minutes. Twenty minutes is a satisfactory rest period for persons who have normal blood pres-

sure. Several readings of blood pressure are taken until a basal level has been approximated. If hypertension is present, a longer period of rest may be necessary to establish a basal level. The blood pressure of a few patients who have severe essential hypertension will remain at fixed high levels and a basal level cannot be secured even after several hours of rest.

With the subject still supine, and with the cuff of the sphygmomanometer on one arm the opposite hand is immersed in ice water (4° C.) to a point just above the wrist. With the hand still in the water, readings of the blood pressure are taken at the end of thirty and sixty seconds, respectively. The highest of the two readings obtained while the hand is in the ice water is taken as an index of the response. The hand is removed from the ice water as soon as the sixty second reading has been made and readings are taken every two minutes until the blood pressure returns to its previous basal level. All of the foregoing matters are of importance and certain additional precautions will now be considered.

Precautions in carrying out the test.—We perform the test with the subject lying down. If other positions are used, the effect of posture must be taken into account in evaluating the results. Sitting or standing will elevate the basal blood pressure, especially the diastolic pressure, and the hydrostatic effects of sitting or standing usually will decrease the reaction to the cold water, especially if subjects have hypertension.

It is well to describe to the patient the nature of the test at the beginning of the rest period so that undue apprehension may be prevented. The temperature of the water should not be less than 3° C. or more than 5° C. and its temperature should be measured just before the subject's hand is plunged into it.

Inasmuch as vasodilator and sedative drugs may reduce the response to the standard stimulus, the subject should not take any of these drugs *within twenty-four hours* before the test is performed. Slowly eliminated sedatives such as bromides may affect the response more than twenty-four hours after their use has been discontinued.

Evaluation of results.—The maximal response may occur within thirty seconds. The blood pressure of subjects whose pressure is usually normal returns to the basal level within two

minutes after the hand has been removed from cold water. In the presence of established hypertension the return of the blood pressure to the basal level may be delayed.

The *diastolic* response to the test is a more reliable index of vasoconstriction than the *systolic* response, but less error will occur if both the systolic and diastolic responses are considered in evaluating the result of an individual test. Inasmuch as the test is a measure of vasoconstrictor response, the systolic reading alone is of questionable value in determining whether the subject has a hyperreactive vasoconstrictor mechanism. As to what constitutes a significant response, analysis of the results of a large number of tests has determined that an elevation above the basal level of more than 20 mm. of mercury in the systolic pressure and of more than 15 mm. in the diastolic pressure indicates a hyperreactive type of response to the rest. If the maximal reading obtained is greater than 140 mm. of mercury, systolic and 90 mm., diastolic, the subject is even more certain to have a hyperreactive vasoconstrictor mechanism.

Ayman and Goldshine have recently described a test which they call "*the breath-holding test*" which they consider to be a simple standard stimulus of blood pressure. They have made a preliminary report of their experience with this test, but its general use as a standard test for blood pressure must await information covering the response of a larger group of subjects. In my experience, it has been more difficult to obtain the complete co-operation of the patient in carrying out the breath-holding test than in carrying out the cold pressor test. The breath-holding test does have the advantage, however, of not requiring any special apparatus such as ice and a container.

The majority of subjects with normal blood pressure have a relatively small variability of the blood pressure with a range of approximately 10 to 20 mm. of mercury in systolic and diastolic blood pressure. Approximately 15 per cent of persons with a normal blood pressure have a marked variability of the blood pressure and excessive reactions of the blood pressure to stimulation. The variability in the blood pressure in this group of "normal hyperreactors" will be approximately two to three times greater than the mean change among the group of "normal reactors."

The systolic and diastolic blood pressures may vary dissimilarly. In some instances, there is considerable change in the systolic pressure and little or no change in the diastolic pressure. However, when there is a marked change in the diastolic pressure, there is usually a similar change in the systolic pressure. It is probable that there is considerable difference in the significance of a rise in the systolic blood pressure alone as compared with a rise in only the diastolic blood pressure. The diastolic response is the more reliable index of vasoconstriction. Changes in only the systolic blood pressure are indicative of increased cardiac output, such as may occur in cases of hyperthyroidism, the effort syndrome and as the result of the effect of adrenalin.

My experience with the cold pressor test has led me to believe that excessive variability and response of the usually normal blood pressure to stimulation is evidence of a *pre-hypertensive phase* of the syndrome which is designated as *essential hypertension* because of the following observations: 1. The hyperreactivity of the blood pressure of the normal hyperreactor is of the same type and frequently is of the same degree as that which is characteristic of 95 per cent of individuals with essential hypertension. 2. Individuals who are known to have had hypertension, but whose blood pressure has been reduced to normal by cardiac failure or by other factors, give a hyperreactive response to the cold pressor test similar to that of the person with hypertension. 3. The incidence of hyperreactors among children approximates the combined incidence of hypertension and hyperreactors among adults. 4. Subjects with usually normal blood pressure, who are hyperreactors generally come from families in which there is a high incidence of hypertensive cardiovascular disease, whereas subjects with normal blood pressure who are hyporeactors generally do not. 5. Thirty-eight per cent of originally normal hyperreactors have experienced the development of hypertension within six years, whereas none of the normal hyporeactors have done so.

Other evidence is accumulating which also indicates that unusual fluctuations of the blood pressure in subjects with usually normal blood pressure is indicative of a prehypertensive state. Robinson and Brucer, following a detailed statistical

and clinical study of a large group of persons, have concluded that the normal range of systolic blood pressure is between 90 and 120 mm. of mercury and that the normal range of the diastolic pressure is between 60 and 80 mm. Diehl and Heschdorffer have observed 155 students for a period of seven years and have found that young men showing even transitory elevation of the blood pressure during their college years are much more likely to have an elevated blood pressure after a period of from five to ten years than are students whose blood pressure was consistently within the normal range. The probabilities of their having hypertension in later years was found to be in direct proportion to the frequency of previous elevation of the blood pressure. In a follow-up study of 1,500 patients with originally normal blood pressures, I have found that the majority (70.4 per cent) of the patients who, as a result of nervous stress, had an original elevation in systolic and diastolic blood pressures into the upper ranges of normal (140 to 150 mm. systolic and 85 to 100 mm. diastolic) had hypertension subsequently (ten or twenty years later); whereas, only a small number (3.4 per cent) with original blood pressures in the lower ranges of normal had hypertension subsequently. None of the patients who had an original systolic blood pressure greater than 140 mm. but who had a diastolic blood pressure of less than 85 mm. had hypertension subsequently. To state this in a different way, of 206 patients who recently had hypertension, 86 per cent gave evidence of hyperreactivity of the mechanism for regulating blood pressure ten to twenty years previously although they did not have hypertension at that time and the majority did not have hypertension until a number of years had elapsed.

The modern conception of blood pressure demands an awareness of the *variability* of the blood pressure and should consider the possible significance of *hyperreaction* of the usually normal blood pressure. Transient elevations of both the systolic and diastolic blood pressures or of the diastolic blood pressure alone should not be ignored. In many cases, such changes in blood pressure are indicative of a prehypertensive stage of essential hypertension. On the other hand, transient elevation of only the systolic blood pressure is not prognostic of subsequent hypertension.

One may well question the advisability of informing a patient of the fact that he has a hyperreactive type of blood pressure and that he is subject to the eventual development of hypertension. However, if the patient understands that it is not known that all hyperreactors will experience the development of hypertension or how many years may elapse before persistent hypertension will occur, undue anxiety can be avoided. In the meantime, the finding of the abnormality of the blood pressure affords the patient an opportunity to make adjustments in his mode of living that may pay good future dividends.

THE IMPORTANCE OF STUDYING THE POSTURAL RESPONSES OF THE BLOOD PRESSURE AND THE HEART RATE, WITH A NOTE ON THE METHOD OF TAKING THE BLOOD PRESSURE IN THE ERECT POSTURE

MAXWELL R. BERRY, JR., BAYARD T. HORTON AND
ALEXANDER R. MACLEAN

The importance of recording a patient's blood pressure and pulse rate not only in the *supine* or *sitting* posture, but while the patient is *standing* cannot be overemphasized. In performing a physical examination it is no more justifiable to record the blood pressure with the patient in one posture only than it would be to examine the patient's thorax by percussion alone, for in neither case would the physician have extracted more than a modicum of the information available to him.

Both the blood pressure and the pulse rate may be normal in the horizontal posture yet distinctly abnormal when the patient stands. It must be recognized that values for the blood pressure and the heart rate are never static, but rather are continually fluctuating in order to provide the individual with optimal adjustment to postural changes, physical exertion, psychic stimuli, metabolic changes, local needs of tissues and the environment.

In this clinic we shall attempt to present general information necessary to an understanding of the mechanisms of poor postural adaptation, stressing the facts that: (1) postural maladaptation may occur in the presence of a variety of diseases, and (2) the simple measure of comparing the blood pressure and pulse rates while the patient is in the supine and erect postures and after exercise, often yields information indicative of unsuspected primary disease.

Before proceeding to a discussion of the postural adaptive mechanisms, it is worth while to review briefly a few of the significant facts concerning the interpretation of blood pressure in general:

SIGNIFICANCE OF THE DIASTOLIC AND SYSTOLIC BLOOD PRESSURES AND THE PULSE PRESSURE

Diastolic blood pressure.—It is generally agreed that the diastolic blood pressure in the normal individual is a measure of the peripheral resistance or an index of the vasomotor tone.^{25, 26, 63, 65} In general, the lower the diastolic pressure, the less the peripheral resistance is and the greater the vasodilation. If the diastolic pressure decreases much when the patient is standing, poor postural adaptation is present.

Pulse pressure.—The pulse pressure depends mainly on the interaction of four factors: (1) the amount of blood pumped by the heart, (2) the peripheral resistance, (3) the elasticity of the blood vessels, and (4) the speed with which the left ventricle contracts.⁶⁷ Therefore, the pulse pressure can serve only as a crude index of any one of these four factors.

Systolic blood pressure.—The systolic pressure is the sum of the diastolic and the pulse pressures and therefore depends on the five different factors on which the aforementioned two pressures depend. If the systolic pressure is well maintained when the patient is in the erect position without undue increase in the cardiac rate, it is obvious that the gravity-resisting mechanisms are fairly normal.¹⁷ If there is an excessive decrease in the patient's systolic pressure on standing, the chain of adaptive mechanisms has broken down in one or more of its links. The malfunctioning link will be found in the cardiac mechanisms,^{26, 47, 63} in the vasomotor mechanisms,^{26, 64} or in the mechanisms by means of which blood is returned to the heart.⁴³

VARIABILITY OF BLOOD PRESSURE IN ONE POSTURE

Ordinarily, when the blood pressure is spoken of, it is considered only in terms of the pressure in the brachial artery. However, the blood pressure varies independently in each of the four extremities and is consistently higher in the popliteal arteries than it is in the brachial arteries in every posture except that in which the patient's head is down.¹⁰

Lately, it has been shown that the yearly and diurnal variations of normal blood pressure with the patient in the sitting posture usually do not exceed, on the average, 10 mm. of mercury, whereas abnormal blood pressures may vary much more.⁵⁷

It is now well known, as Sigler wrote, that "every level of blood-pressure reading fluctuates independently of the other and in a disorderly fashion,"^{63, 66} and numerous studies have revealed the variations in values for blood pressure which occur with postural changes, exercise, sleep, psychic stimulation, ingestion of food and rest. Thus, the hazards of drawing final conclusions from one recording of the blood pressure in one posture become apparent.

WHAT CONSTITUTES NORMAL BLOOD PRESSURE AND PULSE RATE?

Lately it has been stressed increasingly that the old upper limits of normal, that is, 140/90,* are too high.^{2, 35, 57} In fact, the recent study of Robinson and Brucer seems to indicate that any blood pressure value in the sitting posture which is consistently above 120/80 is abnormal, and that values ordinarily considered hypotensive, that is, 90/60 to 100/70, are ideal in so far as life expectancy is concerned. Similarly, pulse rates between 55 and 65 beats a minute indicate a life expectancy well above that indicated by the time-honored "normal" of 72 plus or minus 10. From an actuarial standpoint, therefore, hypotension without postural maladaptation prognosticates longevity.

Thus, by the simple expedient of studying blood pressure and pulse rate with the patient not only in the supine but also in the standing position, an idea can be obtained of the integrity of a whole chain of postural adaptation mechanisms as well as an indication of the life expectancy of the patient. It will be shown later that postural maladaptation occurs in the presence of a wide variety of diseases, and in many of these it not only explains many of the patient's symptoms, but its recognition may constitute the first signpost of disease.

THE POSTURAL ADAPTATION MECHANISMS

Normal responses to standing and the links in the postural adaptation chain.—Despite a formidable amount of investigation, begun as far back as Falconer in 1796,²² our knowledge of these mechanisms is incomplete, and the evalua-

* This convention will be used throughout the text to express the systolic and diastolic blood pressure readings in millimeters of mercury.

tion of much of the work is indeed difficult. We know that man has developed a much more delicate apparatus for combating the effects of gravity than have the four-footed animals. It is not improbable that he has developed new reflexes or drastically modified those which are phylogenetically old in order to compensate for the erect posture. As stressed by Roth,⁶¹ it is therefore unwise to apply the principles evolved from experimentation with animals to man, without reserve.

Normal responses to alteration in posture.—Normal individuals exhibit an increase in the pulse rate and in the diastolic blood pressure, and a slight increase or no change in the systolic blood pressure on changing from the supine to the standing position. Sitting values lie between the horizontal and the erect values. Rough averages for these changes in normal persons are an increase in the pulse rate of about 12 beats a minute, an increase in the diastolic blood pressure of about 12 mm. of mercury, and a change in the systolic blood pressure between an increase or a decrease of 10 mm. of mercury.^{3, 21, 25, 47, 48, 63, 64} Only about a third of normal people will exhibit an increase in the systolic and diastolic blood pressures and the pulse rate, on standing.²¹

Immediately after standing, there is a sharp decrease in the systolic blood pressure amounting to from 5 to 40 mm. of mercury within the first ten seconds. This is the result of the gravitational flow of blood downward. In about 75 per cent of normal people the diastolic blood pressure increases in the first ten seconds. Thirty seconds after standing, the systolic value is usually higher than the reclining value. The adaptive mechanisms have overcompensated, whereas at sixty seconds the systolic pressure, diastolic pressure and pulse rate have become stabilized as discussed in the preceding paragraph.⁷⁰

The venous-return and cardiac-output links and the effect of prolonged standing.—That prolonged standing exerts a severe strain on the circulation is proved by the fact that many normal individuals will faint if they stand motionless for long periods of time.^{69, 70} This action is undoubtedly a manifestation of cerebral anemia caused by decreased venous return to the right side of the heart secondary to a lack of the muscular contractions and relaxations which normally massage the venous blood toward the heart. Henderson²³ strongly sup-

ported this view and believed that muscular tonus, especially that of the diaphragm, abdominal muscles and the intestines is equally as important as the peripheral vasomotor tonus in maintenance of the blood pressure while the individual is standing. Furthermore, it has been repeatedly emphasized, to quote Starr and associates,⁶⁸ that "The heart's output, and indeed its work also, is limited by the amount of blood returned to it through the veins. If this is inadequate, no effort on the part of the heart can increase the circulation." A majority of the investigators have found that the cardiac output is decreased when the individual is standing.^{10, 45}

Thus, if it is difficult for even the normal individual to maintain his circulation while erect, it is small wonder that malfunction of the apparatus for combating the effects of gravity leads to pronounced symptoms when standing which may disappear when such an individual lies down.

Exercise often will reveal postural maladaptation in patients whose standing blood pressures and pulse rates are at the borderline of normal. In the first case reported by MacLean, Horton and Moersch,⁴³ the patient's standing blood pressure was 100/70 and the pulse rate 125 beats a minute. After the patient had walked twenty steps, the blood pressure was 90/75 and the pulse rate 160.

The relationship of the splanchnic bed and the lower limbs to the gravitational flow of blood.—When a person stands or sits, blood tends to gravitate to the structures which are situated below the level of the heart in such a position, engorging the splanchnic bed and the lower limbs. If the postural adaptive mechanisms fail adequately to resist the gravitational flow, temporary cerebral anemia results. The position in which the patient's head is low will immediately compensate for failure of the postural adaptation reflexes.^{33, 34, 51}

Roth's^{60, 61} study has demonstrated conclusively the importance of the splanchnic bed and the lower limbs in the maintenance of the circulation while the individual is standing. Roth showed that the most important reflexes for maintaining the blood pressure when erect are (1) those mediated through the splanchnic nerves which largely govern the flow through the splanchnic bed and, (2) those mediated through the vasomotor sympathetic fibers arising in the upper lumbar region,

which largely control the flow of blood through the lower extremities.

Thus it becomes clear why the use of such mechanical measures as a tight abdominal binder,^{20, 33} and cuffs about the thighs will tend to prevent a marked decrease in the blood pressure while the patient is standing. External pressure, instead of vasomotor tonus, tends to prevent pooling of blood in these regions.

When the vasomotor mechanisms are intact, the splanchnic bed and the lower limbs form a variable resistance control for the circulation and are amply sufficient to compensate for the hydrostatic effects of gravity.³⁴

MacWilliam reasonably assumed that the alteration in pulse rate and blood pressure when a person changes from the sitting to the erect posture cannot be attributed to a difference in the incidence of gravity acting on the splanchnic bed, since the force of gravity exerted on this region is about the same in each of the aforementioned postures. However, the hydrostatic effect of gravity probably does account for a part of the alteration of blood pressure and pulse rate found in a patient's changing from the supine to the sitting posture and vice versa.

THE VASOMOTOR CENTERS AND THE SPINAL PATHWAYS

It is probable that, in human beings, all the vasomotor reflexes must pass through cerebral centers in completing the reflex arc.^{20, 50} Cerebral vasoconstrictor and vasodilator centers lie in the nuclei of the hypothalamus^{24, 52, 54} with some measure of control situated in the premotor region of the cerebral cortex.^{6, 20, 24} It is as yet debatable whether alterations in the cerebral blood pressure act directly on the cerebral vasomotor centers. The tonus of the vasomotor centers is maintained chiefly by the arterial carbon-dioxide tension and is modified by reflexes mediated through the carotid sinus and aortic nerves.^{7, 18, 23}

There are not only vasoconstrictor pathways but also vasodilator (inhibitory) pathways which have different anatomic situations and characteristics within the spinal cord.^{27, 49, 53} The vasoconstrictor afferent path is bilateral and chiefly uncrossed, lying in the apices of the posterior horn, whereas the vasodilator afferent path is chiefly crossed and lies in the lateral funiculus.⁵⁵

The vasoconstrictor efferent fibers arise from cells lying in the lateral horns of the spinal cord between the first thoracic and the fourth lumbar segments, inclusive.⁶ The efferent path follows two separate routes: a proximal route lying along the great blood vessel trunks and supplying only the trunks and larger branches, and a distal route lying in the somatic nerve trunks, such as the sciatic and the ulnar, supplying only the smaller branches of the large arterial trunks.³⁹

The splanchnic bed is controlled chiefly by fibers running in the greater and lesser splanchnic nerves and fibers from the plexuses about the abdominal aorta. The origin of these is from the fifth thoracic to the twelfth thoracic segments, inclusive. These sympathetic nerves carry no parasympathetic sweating components. The vasomotor control for the lower limbs has its origin from the twelfth thoracic to the fourth lumbar segments, inclusive. These vasomotor sympathetic nerves carry parasympathetic fibers which control sweating, as do the vasomotor nerves of most of the rest of the body.⁵⁹

Therefore, involvement of the central nervous system in many diseases may induce postural maladaptation. In lesions of the sympathetic vasomotor nerves, except for the splanchnic nerves, anhidrosis should be found in corresponding regions as worked out by Roth.⁶²

The carotid sinus reflex and the aortic cardio-depressor nerve (buffer nerves).—Alterations in the blood pressure within the carotid arteries stimulate nerve endings lying in the carotid sinuses and produce profound reflex circulatory changes in the individual. These changes may be artificially produced by digital pressure on the bifurcation of the carotid arteries. This causes a marked slowing of the heart rate, vasodilation, and a decrease in the blood pressure by raising the intracarotid pressure. Occlusion of the common carotid arteries more proximally, by reducing the intracarotid blood pressure, accelerates the heart rate, causes vasoconstriction and an increase in arterial blood pressure.⁶

People often react differently to mechanical stimulation of the carotid sinuses and Weiss and his colleagues⁷² have classified the different reactions as: (1) the vagal type, characterized by sino-auricular or auriculoventricular nodal block; (2) the depressor type, characterized by a marked decrease in the blood pressure unassociated with cardiac arrhythmia; and (3)

the cerebral type, in which syncope occurs without changes in the cardiovascular system or in the total flow of blood through the brain.

The afferent limb of the carotid sinus reflex is the sinus nerve (a branch of the glossopharyngeal nerve) which sends fibers to both the cardio-inhibitory and the vasomotor centers. The efferent limb is formed of sympathetic fibers passing in the sympathetic vasomotor and the vagus nerves.^{12, 31, 32, 38, 60, 71}

It is probable that for some people the carotid sinus reflex is of less importance in the maintenance of blood pressure in the erect position than it is for others. The carotid sinus may be so sensitive to external pressure that shaving the neck will induce syncope and convulsions. Individuals who have such a condition may be cured by denervation of the carotid sinus.¹⁴ In about 30 per cent of normal people the carotid sinus reflex is entirely insensitive to digital pressure.⁷¹

The aortic nerve.—The aortic nerve is purely cardio-inhibitory; it arises as a collection of the cardiac depressor fibers of the vagus nerve. An increase in pressure in the arch of the aorta causes slowing and weakening of the heart beat and vasodilation, especially of the splanchnic bed. The efferent limb of the reflex for the cardio-inhibitory fibers is the vagus, and the vasomotor pathways for the vasodilation component.⁹

Therefore, slowing of the heart rate and decrease in blood pressure when an individual is supine may be caused in part by stimulation of the carotid sinus and aortic nerves by increased pressure within the carotid artery and aorta. In fact, MacWilliam stated that, "The parallelism between (1) carotid sinus reflex activity as tested by mechanical pressure and (2) the slower or quicker rates associated with the lying or sitting postures respectively, has been found to be so definite and constant that recognition of (1) enables one to predict the behavior of (2) and *vice versa*." Similarly, when an individual changes from the supine to the erect posture, the immediate decrease in blood pressure that occurs probably induces some measure of vasoconstriction mediated through the carotid sinus reflex.

THE BAINBRIDGE REFLEX

This is a mechanism by means of which increased venous pressure in the right auricle and vena cava evokes afferent impulses which reflexly accelerate the heart rate. It is evi-

dently the physiologic means by which the heart is able to rid itself of the excess blood reaching it. The afferent limb of the reflex arc travels in the vagus nerve to the cardiac center.⁸

Other reflexes.—MacWilliam postulated the presence of a reflexogenic system within the great vessels of the thigh, activated by alterations in the relationship of the thigh to the vertical position. These alterations supposedly modify the heart rate and the blood pressure. The reflex is inactive when the trunk is horizontal. In MacWilliam's opinion, none of the other mechanisms can account so adequately for the increase in the pulse rate on the individual's changing from the sitting to the erect posture.

MacWilliam also noted in one case that muscular cramps induced an increase in the pulse rate (72 to 90 beats a minute) entirely out of proportion to the pain produced by the cramp. He therefore believed that the muscles themselves may give rise to afferent impulses which modify the pulse rate.

THE CHEMICAL TRANSMISSION OF NERVE IMPULSES

This relatively new field is still largely unexplored. However, experimental evidence demonstrates the chemical nature of the transmission of the nerve impulse at the synapse and end organ of the peripheral sympathetic and parasympathetic nervous system.^{23, 24} Obviously, if there is blocking of the nerve impulse at the synapse or end organ, the reflex arcs are as completely inactivated as if their conducting nerves had been transected.

The synaptic transmission of nerve impulses within the central nervous system is probably primarily electric in nature. On the other hand, the transmission between the preganglionic and postganglionic fibers within the sympathetic ganglion is considered to be mediated by acetylcholine, the preganglionic sympathetic nerve impulse causing the formation of acetylcholine at the synapse. Acetylcholine transmits the nerve impulse through the synapse to the postganglionic neuron. The postganglionic (adrenergic) nerve impulse stimulates the formation, at the end organ, of an adrenalin-like substance tentatively called "sympathin," which in turn transmits the impulse from the postganglionic fiber to the muscle or gland to be activated.

The peripheral parasympathetic (cholinergic) nerve impulses are mediated solely by acetylcholine, the ganglia in this instance being situated at the end organs. Thus, acetylcholine appears to transmit the nerve impulse through the sympathetic nerve ganglia and through the parasympathetic end organs to the effector organs—muscle or gland. Sympathin transmits the nerve impulse through the sympathetic end organ to the effector organ.

Choline-esterase is a substance found in practically all tissues of the body, end organs, sympathetic ganglia, and brain. This substance inactivates acetylcholine rapidly, thereby preventing acetylcholine from acting more than a short time. Atropine acts primarily on the parasympathetic end organs, blocking the transmission of nerve impulses.

Physostigmine and $C_{13}H_{22}O_6N_2S$ (prostigmin) inhibit choline-esterase, allowing the acetylcholine to act freely, uninhibited by choline-esterase. Ephedrine and epinephrine act primarily by enhancing the action of sympathin at the sympathetic end organs.

DISEASES IN WHICH POSTURAL MALADAPTATION MAY PLAY A RÔLE

(With Case Reports to Illustrate the Various Links in the Postural Adaptation Chain)

A frequent misconception is the one that holds that postural studies will enable the physician to diagnose only one condition: idiopathic postural (orthostatic) hypotension. The falsity of this belief is revealed in the wide variety of primary pathologic entities in which postural maladaptation has been reported to have been present: Addison's disease, diabetes mellitus, tabes dorsalis, syringomyelia, hematomyelia, exhaustion states, myasthenia gravis, abdominal injury, transection of the cervical portion of the spinal cord, psychoneurosis, major sympathetic operations, and systemic infections.

IDIOPATHIC POSTURAL (ORTHOSTATIC) HYPOTENSION, ILLUSTRATING THE IMPORTANCE OF THE SPLANCHNIC BED

The major signs and symptoms of this entity have been reported as being^{4, 8, 11, 40}: (1) a sharp decrease in the systolic and diastolic blood pressures when the patient stands, in all

cases in which there is syncope or marked weakness, (2) deficient sweating, either localized or generalized, (3) failure of the pulse rate to increase markedly when the patient assumes the erect posture, (4) accentuation of symptoms in hot weather, and (5) secretion of more urine in the recumbent than in the erect posture. Other relevant signs and symptoms were reported as: (1) appearance of youthfulness in the patient, (2) slightly lowered basal metabolic rate, (3) signs of organic change in the nervous system, (4) loss of libido, perhaps accompanied by impotency, (5) pallor of skin and (6) concentration of blood urea at the upper limits of normal.

A wide variety of drugs has been used to elevate the blood pressure.^{26, 27, 38, 40} Of these, ephedrine probably is the best for those patients who can tolerate it. Pilocarpine will induce sweating in the anhidrotic areas,⁴ while reflex heat vasodilatation will not. Two of us (MacLean and Horton) have stressed the importance of a trial of prostigmine in all cases of orthostatic hypotension.⁴²

The situation of the lesion in idiopathic postural hypotension is as yet unknown. However, the majority of evidence points toward two sites: (1) the acetylcholine transmission of nerve impulses through the sympathetic ganglia and the parasympathetic end organs, and (2) the sympathetic and parasympathetic pathways within the central nervous system.

The distribution of regions of anhidrosis found in most cases of idiopathic orthostatic hypotension follows closely that produced by section of the anterior roots of the spinal cord and sympathetic ganglionectomy.⁶² The autonomic nerve supply to the sweat glands is anatomically sympathetic, but is pharmacologically parasympathetic.⁴² Thus the disease in question affects both the sympathetic and the parasympathetic components of the autonomic nervous system.

Case I.*—A seventy-year-old white man entered The Mayo Clinic on September 13, 1938, complaining of weakness and dizziness. He had always been asthenic, although in excellent health except for influenza which had afflicted him in 1918, and appendicitis for which appendectomy had been performed in 1914.

About five years before admission he had noticed dizziness and weakness for the first time. The latter appeared especially in the morning after arising

* Previously reported.

and the former on standing after he had been recumbent or sitting for some time. Actual syncope occurred at times. Until the year before admission, attacks had been occasional, but by the time that he was seen, many attacks would occur during the course of a day. Relief invariably could be produced by bending over while standing or by lying down. He stated that he excreted a larger volume of urine at night than during the day. No history of anhidrosis could be elicited and in fact the patient believed that attacks were more frequent and severe in the winter than in the summer.

On physical examination the patient appeared to be at least ten years younger than his actual age. A minimal amount of arteriosclerosis was present; there was no graying of the hair, and the skin showed few senile changes. The tonsils were chronically infected. Periapical dental infection was graded 2 and pyorrhea alveolaris graded 1, on a scale in which 1 indicates minimal and 4 extreme involvement. The carotid sinus reflex was not hyperactive to digital pressure. Mild emphysema was present as was also a soft precordial systolic

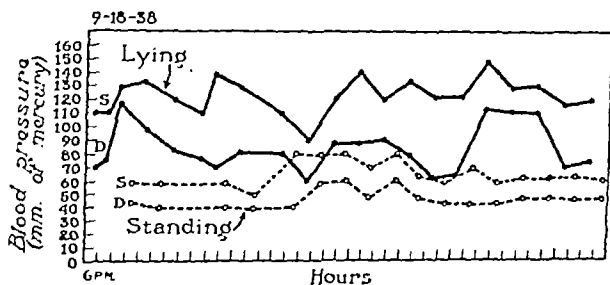


Fig. 134.—Hourly readings of blood pressure over a period of approximately forty consecutive hours. Solid lines indicate blood pressure with patient recumbent and dotted lines, with patient standing. S indicates systolic and D, diastolic.

murmur. The abdomen was normal except for poor muscular tonus. The prostate gland was enlarged, grade 1, and prostatitis, grade 1, was present. There were moderate tortuosity and sclerosis of the peripheral arteries. Results of neurologic examination were essentially normal.

The results of most of the laboratory tests were normal. The value for urea nitrogen was at the upper limits of normal, being 42 mg. per 100 c.c. of blood. Basal metabolic rate was +6.

Various procedures were then performed with the patient's co-operation: First, hourly blood pressure readings with the patient in the erect and recumbent postures were taken over a period of 40 hours. The results are shown in Fig. 134. Second, daily blood pressure readings were taken for six days with the patient in the recumbent and erect postures. The results are shown in Fig. 135. Third, the patient was placed semirecumbent at an angle of 45 degrees on the tilt table. At intervals of three minutes, intravenous injections of 12.5 mg. of ephedrine sulfate were administered until a total of 100 mg. had been injected. At the outset of this procedure the blood pressure was 70/60 and

the pulse rate was 60. At the end of the procedure the blood pressure was 84/60 and the pulse rate was 100. The patient could stand and walk without dizziness or weakness. Fourth, sweating was induced with a baker and perspiration was found everywhere on the body except for a small region on the inner aspect of each leg. Fifth, urine passed during the day and night was collected separately. The average diurnal output was 500 c.c., and the average nocturnal output was 900 c.c. Sixth, a tight abdominal binder was applied whenever the patient walked; this binder seemed to reduce the tendency toward syncope. Marked giddiness and weakness on the patient's standing were present when the binder was removed.

On a schedule calling for the administration of ephedrine sulfate, 25 mg. at 6, 7 and 8 o'clock, in the morning, at noon, and at 3 o'clock in the after-

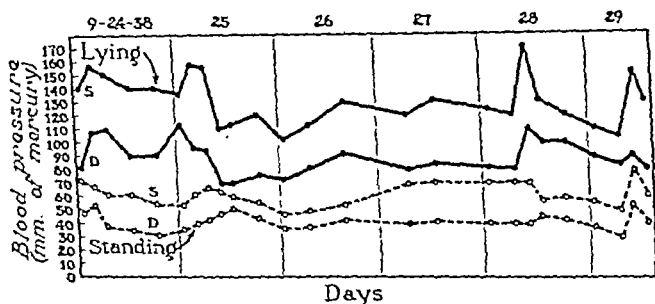


Fig. 135.—Observations on blood pressure plotted as in Fig. 134, but at less frequent intervals, over a period of approximately six days.

noon, the patient improved remarkably and on dismissal his blood pressure while he was sitting was 100/70, while he was standing, 76/50, and while he was supine, 142/90.

Comment.—This case illustrates graphically the fact that the postural adaptability of the vasomotor system and the mean blood pressure cannot be estimated by one blood pressure reading taken with a patient in any one posture. The blood pressure when the patient was in the supine position frequently ranged in hypertensive values and fluctuated between 170/110 and 92/64. The blood pressure, while the patient was standing, showed much less fluctuation and frequently approached a shock value. It is interesting that the patient revealed no abnormality of sweating and we may, therefore, assume that the vasomotor control of the splanchnic bed was specifically involved, since, of all the vasomotor nerves the greater and lesser splanchnic nerves alone have no sweating reflex com-

ponent. It might be assumed also that the sympathetic nerves producing cardiac acceleration were intact, since the cardiac rate could be elevated from 60 to 100 by ephedrine sulfate. The fact that relatively enormous doses of ephedrine raised the patient's standing blood pressure but little (though indeed enough to yield marked symptomatic improvement) would seem to indicate either inability of a uniformly damaged vasoconstrictor reflex to react more than minimally, or a spotty affection of the individual sympathetic effectors. In the latter case, ephedrine probably would have had no reaction on the inactivated effectors but would have had a maximal reaction on those which remained normal.

CONSTITUTIONAL INFECTIONS, ILLUSTRATING THE IMPORTANCE OF THE GENERAL VASOMOTOR TONUS

Crampton^{15, 16, 17} long ago pointed out that even mild infections would almost invariably induce a greater decrease in blood pressure when the patient was standing than would occur when the subject was free of infection. Sewall in 1919 amply confirmed this.^{64, 65}

Case II.—A white man about fifty years old entered the Clinic because of increasing thirst and mild tendency toward becoming tired. Glucose tolerance tests revealed mild diabetes mellitus, although the urine usually was free of sugar. Postural studies concerning the patient were made for two successive days. On the first day after breakfast, the patient's blood pressure increased slightly on standing, after being in the recumbent position. After lunch the patient's systolic blood pressure decreased slightly when he stood. During the afternoon the patient played eighteen holes of golf and a short while later a decrease of about 10 mm. of mercury in systolic blood pressure occurred. These reactions were essentially normal. On the second day, the response after breakfast was entirely normal. However, at 5 p.m. the patient's systolic pressure decreased about 20 mm. of mercury on his standing, and the patient stated that he did not feel so fit as he had during the preceding day. The following morning the patient awoke with a severe common cold.

Comment.—Evidently, the vasomotor system is a delicate barometer of the state of fitness of a given subject. Systemic infections almost invariably lower the general vasomotor tonus. Many athletic coaches throughout the country routinely use postural tests (the Crampton index or modifications of it) to select the athletes who will compete.

MAJOR OPERATIONS ON THE SYMPATHETIC NERVOUS SYSTEM, ILLUSTRATING THE IMPORTANCE OF VASOMOTOR CONTROL OF THE LOWER LIMBS AND SPLANCHNIC BED

Case III.—A young woman of thirty years entered The Mayo Clinic for complaints referable to essential hypertension and migraine. She was admitted to St. Mary's Hospital for study. The day after admission postural studies were done, and were done again ten and twelve days after extensive sympathectomy with removal of a portion of the celiac ganglion, section of the splanchnic nerves, removal of the first and second lumbar sympathetic ganglia, and the intervening trunks. The results are shown in Table 1, in which it is ob-

TABLE 1

BLOOD PRESSURES AND PULSE RATES BEFORE AND AFTER SYMPATHECTOMY;
PATIENT WHO HAD ESSENTIAL HYPERTENSION AND MIGRAINE

	Lying.		Standing.	
	Blood pressure.	Pulse rate.	Blood pressure.	Pulse rate.
Preoperative.....	164/120	72	155/126	92
10 days postoperatively.....	138/100	88	78/ 64	
12 days postoperatively.....	128/98	..	82/ 60	

vious that the patient after operation has marked orthostatic hypotension which did not exist prior to operation.

Comment.—Since major operations other than those performed on the sympathetic nervous system do not materially affect the blood pressure,⁶⁰ it is obvious that the postural adaptation reflexes of this patient were remarkably impaired by operation. A postoperative sweating test revealed anhidrosis to the upper portion of the mid thigh, bilaterally, thus confirming the approximate extensiveness of the interruption of the vasomotor control for the lower limbs. Section of the splanchnic nerves and partial celiac ganglionectomy effectively eliminated the splanchnic link of the postural adaptation chain.

PSYCHONEUROSIS WITH EXHAUSTION, ILLUSTRATING THE IMPORTANCE OF THE VENOUS RETURN AND CARDIAC OUTPUT LINKS OF THE POSTURAL ADAPTATION CHAIN

Case IV.—A thirty-six-year-old unmarried school teacher entered St. Mary's Hospital complaining of abdominal pain referable to a renal calculus, and many symptoms pointing to a diagnosis of psychoneurosis. Three years

ago she had become extremely nervous during a grueling schedule of study at summer school. A few months later she had noted anorexia, abdominal bloating and had become constipated. Two years previous to her coming to the hospital she had become ill with influenza, which persisted for nine days, and although the illness was mild, it left her completely exhausted. Family conflicts had occurred shortly afterward, and the patient had begun to experience attacks of "nervous shaking." Ten months prior to her coming to the hospital the death of her father had precipitated a nervous breakdown of the manic-depressive type. She had taken to bed and had remained there until her admission to the hospital here, complaining that she became so exhausted that she could hardly raise her arms when she attempted to get up and about.

Postural studies revealed mild postural maladaptation, as evidenced by too great a decrease in the patient's systolic and diastolic blood pressure values and an undue increase in her heart rate on standing. She was placed on a regimen of $C_{12}H_{21}O_6N_3S$ (prostigmin), crystalline vitamin B_1 (thiamin chloride) and graduated exercises (Table 2). The patient's subjective improvement on this

TABLE 2

EFFECT OF TREATMENT WITH GRADUATED EXERCISES, THIAMIN CHLORIDE AND $C_{12}H_{21}O_6N_3S$ (PROSTIGMIN) ON THE POSTURAL ADAPTATION IN A CASE OF PSYCHONEUROSIS WITH EXHAUSTION

Date.	Treatment.	Lying.		Sitting.		Standing.	
		Blood pressure.	Pulse rate.	Blood pressure.	Pulse rate.	Blood pressure.	Pulse rate.
11/24/39	None.	104/84	84	88/75	96	86/76	104
12/ 6/39	Graduated exercises, prostigmin, thiamin chloride.	102/68	65	96/68	80	98/72	93

regimen is revealed by the fact that her pulse pressure taken while she was standing increased about 12 mm. of mercury, whereas the pulse rate decreased about 10 beats a minute after eleven days of treatment. The effect of prostigmin in this case is not clear-cut and the drug was probably without effect on this patient. Work now in progress seems to indicate that prostigmin is of value in the treatment of some of these patients.

To determine whether the vasomotor system of the patient was intact, a sweating test was done. No regions of anhidrosis could be found. Thus, we could assume that only the adrenergic component was involved.

To locate the nidus of the patient's postural maladaptation, cuffs were placed about the thighs and the circulation to the lower limbs was occluded.

As shown in Table 3, the reaction of this patient to standing was entirely normal with the legs eliminated from the vascular circuit, for no blood could pool in the lower limbs. A tight abdominal binder did not aid much.

Therefore, we may assume that in this patient: (1) the vasomotor control of the lower limbs was organically intact, since no anhidrosis could be demonstrated, (2) either compensatory vasoconstriction did not occur when the patient stood, or venous return from the lower limbs was impeded, since occlusion of the circulation to her lower limbs rendered her postural responses normal, (3) the splanchnic bed played little part in the patient's postural maladaptation, since an abdominal binder did not help, (4) the specific response of myasthenia gravis to prostigmin was absent in this patient, and (5) since the sympathetic vasomotor nerves to the lower limbs were intact, the patient's

TABLE 3

EFFECT OF PLACING CUFFS ABOUT THE THIGHS AND APPLYING A TIGHT ABDOMINAL BINDER IN A CASE OF PSYCHONEUROSIS WITH EXHAUSTION

Without and with thigh cuffs.	Posture.	Blood pressure.		Pulse.
		Systolic.	Diastolic.	
Without thigh cuffs.	Prone.	102	70	65
	Standing.	90	76	98
With cuffs inflated.	Standing.	110	84	85
Cuffs suddenly released.	Standing.	80	70	95
3 minutes after cuffs released.	Standing.	90	80	98
Cuffs inflated and abdominal binder.	Standing.	102	84	81
Cuffs suddenly released.	Standing.	80	74	98
Abdominal binder suddenly released.	Standing.	82	66	102

primary trouble probably was situated in the venous return to the heart, because of poor muscular tonus. Therefore, the treatment included graduated exercises to increase muscular tonus.

MYASTHENIA GRAVIS WITH POSTURAL MALADAPTATION (THE CHEMICAL-TRANSMISSION-OF-NERVE-IMPULSES LINK)

Case V.—A thirty-nine-year-old white man entered The Mayo Clinic on June 21, 1939, complaining of being "all worn out" for the past year. Prior to that time his general health had been good except for headaches and transient lumbar backaches. His mother died at the age of sixty years, of diabetes mellitus, and a brother was said to have had epilepsy. The patient had had diph-

theria, typhoid fever and scarlatina as a child and influenza in 1917 without complications. Recurrent attacks of tonsillitis had occurred for many years and he had had one attack of appendicitis for which appendectomy had been performed in 1926. In January of 1937 the patient had begun to experience attacks of paroxysmal tachycardia in which the pulse rate would increase to 180 beats a minute. Attacks had occurred almost every day for five months but had not recurred thereafter. About two years prior to his registration he had found that he was unable to stand heat well, and at the time he was seen, he dreaded the summer. About one year before admission he had noticed

TABLE 4

BLOOD PRESSURES AND PULSE RATES, AFTER EXERCISE WITHOUT MEDICATION, AND AFTER EXERCISE WITH MEDICATION WITH PROSTIGMIN, ADMINISTERED SUBCUTANEOUSLY

Medication.	Exercise.	Posture.	Blood pressure.		Pulse rate.
			Systolic.	Diastolic.	
None.	None.	Recumbent.	130	88	72
None.	None.	Standing.	125
None.	After walking.	Standing.	160
Prostigmin 1 mg.	None.	Recumbent.	104	70	64
18 hours after.	None.	Standing.	106	80	78
18 hours after.	None.	Sitting.	112	76	68
18 hours after.	$\frac{1}{2}$ minute after exercise.	Standing.	118	72	136
	$\frac{3}{4}$ minute after exercise.	Standing.	120	78	120
	5 minutes after exercise.	Standing.	116	84	84

numbness and tingling in the soles of the feet, a sensation which had gradually progressed upward until the lower leg had become affected to midshin. His feet and hands became cold and clammy intermittently about a year before admission and this symptom became constant about two months later. Sexual weakness began about a year before admission. Ten months before one of us first saw the patient, generalized weakness and fatigue had begun insidiously and had progressed rapidly until at the time of admission, the patient could walk only one or two blocks before his knees became too weak for him to proceed. Sitting for ten to twenty minutes relieved the weakness and fatigue. Four to five weeks before admission the patient had begun to experience dizzy

spells which lasted a few seconds and which occurred about twenty times in all. Looking upward or turning the head rapidly would induce the dizziness. About a month before admission the patient had noticed that his heart would pound rapidly at even slight exercise. So long as he lay in bed, he felt well, but his troubles began when his feet reached the floor.

Results of the patient's physical and neurologic examinations were essentially normal except for the demonstration of chronic tonsillitis. The urine contained occasional pus cells and the sedimentation rate was at the upper limit of normal. The concentration of hemoglobin, erythrocyte, leukocyte and differential counts, roentgenograms of the thorax and head, the cerebrospinal fluid and its dynamics were normal. Results of the Kolmer and Kline tests and the Wassermann reaction were negative. The urine contained no lead or arsenic. The dramatic improvement in the patient's condition which followed administration of 1 mg. of prostigmin subcutaneously is reflected in the improvement of his postural adaptation as shown in Table 4.

The patient's reaction to the Hines-Brown test (standard cold stimulus) was normal. He was put on a regimen of 30 mg. of prostigmin by mouth after breakfast, at noon, 4 o'clock in the afternoon and after supper, and was relieved of most of his symptoms for several weeks, at the end of which time the effects of the drug became less marked. Tincture of belladonna increased the effects somewhat, but it later became necessary to add guanidine hydrochloride. At the time of writing, the patient is following a regimen of prostigmin, 30 mg. being taken orally after meals, and guanidine hydrochloride, 0.5 gm. dissolved in distilled water and taken by the patient orally on arising and at noon.

Comment.—This case reveals the fact that postural maladaptation may occur without undue change in blood pressure when the patient is standing. The pulse rate of this patient, however, reflected the strain on the cardiovascular system. Exercise, by imposing a further burden on the circulation, dramatically revealed the patient's postural maladaptation. As two of us (MacLean, Horton) have pointed out, there is evidence that almost 30 per cent of patients who have myasthenia gravis also will have postural maladaptation. This fact led to the diagnosis and relief of the patient involved in the preceding report. Further work to be published soon indicates that idiopathic orthostatic hypotension frequently has a myasthenic component.⁴¹

DIABETES MELLITUS WITH POSTURAL MALADAPTATION

Case VI.—A seventeen-year-old white woman entered The Mayo Clinic because of uncontrolled diabetes mellitus. On admission there was a definite acetone odor to the patient's breath and a high sugar content in the fasting blood and in the urine. The degree of her diabetes was estimated as being severe. After about two days of hospitalization, the diabetes was well under

control and the patient apparently was normal in every respect except for slight listlessness. Four days later postural study of the patient's blood pressure and pulse rate showed the following: the blood pressure when the patient was recumbent was 128/95 and the pulse rate was 85. On her standing for one minute, the blood pressure was not altered materially, being 119/91 at the end of that time. However, the pulse rate had increased to 132 beats a minute. Cuffs placed about the patient's thighs decreased the pulse rate to 114 beats a minute, and sudden release of the cuffs decreased the blood pressure to 115/80 and increased the pulse rate to 142 beats a minute. The sweating test of Roth showed normal sweating throughout.

Comment.—In 1937, Morgan, Vonderahe and Malone¹⁰ demonstrated pathologic changes in the hypothalamus of a high percentage of patients who had diabetes mellitus. The changes were manifested mainly by the fact that many of the cells had disappeared. The aforementioned investigators were unable to state whether this change was primary or secondary to the diabetes. It is probable that the postural maladaptation of the patient concerned in the preceding report was secondary to depletion of vital resources of the body occurring as a result of uncontrolled diabetes, rather than as the result of destruction of hypothalamic neurons necessary to completion of the vasomotor reflex. It was previously shown that systemic infections such as the common cold could induce postural maladaptation and similarly, depletion of the chemical resources of the body probably can produce difficulty in standing. Ghrist²³ found that about 50 per cent of diabetic patients gave a history of weakness and faintness or dizziness on standing. If postural maladaptation is found in the general physical examination, the cause should be sought after assiduously.

ADDISON'S DISEASE WITH POSTURAL MALADAPTATION

Ghrist also pointed out that about 30 per cent of patients having proved Addison's disease would show blood pressure readings in the erect posture which were close to syncope values. The hypotension which occurs in association with Addison's disease has long been known. Table 5 illustrates the effect on the blood pressure and pulse rate of adequate treatment with sodium chloride and cortin of a woman twenty-nine years old who had severe Addison's disease.

The postural maladaptation of this patient probably is another example of the effects of depletion in the body of vital

chemicals. Epinephrine normally "boosts" the transmission of nerve impulses at the sympathetic end organs, and deficiency of epinephrine may play a part in Addison's disease. Although

TABLE 5

EFFECT OF CORTIN AND SODIUM CHLORIDE ON PULSE RATE AND BLOOD PRESSURE OF PATIENT WHO HAD SEVERE ADDISON'S DISEASE*

Medication.	Posture.	Blood pressure.		Pulse rate.
		Systolic.	Diastolic.	
None.	Recumbent.	66	48	68-76
	Standing.	42	20?	148
	Sitting.	38	28	
After cortin and NaCl.	Recumbent.	91	70	108
	Standing.	98-92	80-52	108
	Sitting.	88	50	100

* The Hines-Brown cold test was normal both before and after treatment.

there is no proof as yet, postural maladaptation may well be the earliest physical manifestation of Addison's disease.

TAKING THE BLOOD PRESSURE IN THE ERECT POSTURE

Recently, a joint committee of the American and British Heart Associations advocated definite technics for recording the blood pressure with the patient in the sitting and recumbent postures.¹⁸ No technic was recommended for determining the blood pressure when the patient stands, however, and therefore it is worth while to consider whether the technic advocated for the sitting posture is applicable to the erect postures.

From reports in the literature, most of the blood pressure determinations in the erect postures have been obtained with the patient's arm pendent at the side in contradistinction to the recommendations of the heart association that the forearm be supported horizontally at the level of the heart. It has long been known that there is a progressive decrease in the blood pressure reading when the patient's arm is progressively

moved from the pendent to the horizontal position.³⁶ This is shown in Fig. 136. The blood pressure readings shown were determined in twelve normal recumbent subjects as advised by the Cardiac Society of Great Britain and Ireland. The average reading for the group was 117/74 mm. of mercury. The subjects then stood quietly and the blood pressure was determined by the usual method with the patient's arm pendent. The aver-

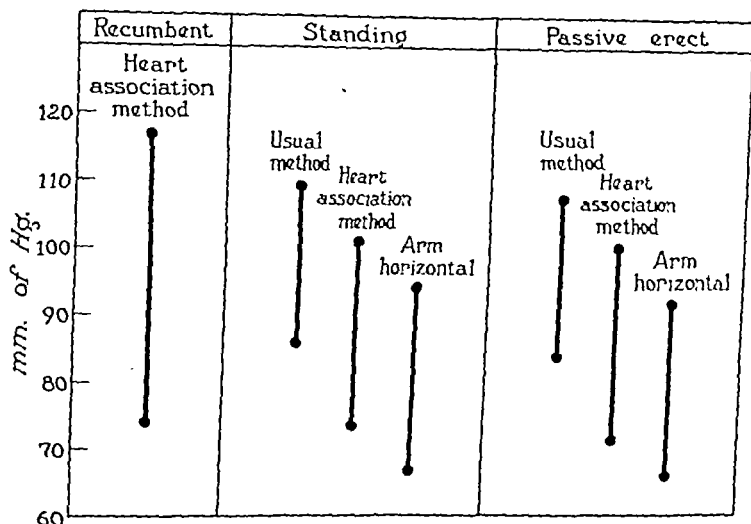


Fig. 136.—Twelve normal subjects. Supine posture: average blood pressure reading by the method of the Cardiac Society of Great Britain and Ireland. Standing posture: blood pressure determined by the usual technic with the patient's arm pendent; with the forearm supported at the level of the heart as advised by the American Heart Association for the sitting posture; with the arm supported while horizontally extended from the shoulder. Passive erect posture.

age reading for the group was found to be 110/86. The forearm was then supported at the level of the heart as recommended by the American Heart Association for the determination of the blood pressure while the patient is in the sitting posture. The average reading for the group was now 100/72 mm. of mercury. When the patient's arm was supported while extended horizontally from the shoulder, the average reading for the group was 94/67 mm. of mercury. Blood pressure readings with the patient in the passive erect posture were

comparable. Thus, a range of 16 mm. of mercury in the systolic reading and 19 mm. of mercury in the diastolic reading was obtained in the erect postures by moving the patient's arm from the pendent to the horizontal position. When the forearm was supported at the level of the heart, the diastolic blood pressure reading of the group was almost identical, in the standing and passive erect postures to that in the recumbent posture.

When the forearm is supported at the level of the heart, the column of blood ascending from the heart to the axillary artery and that descending from the axillary artery in the arm are about equal. Therefore, the hydrostatic force of gravity on these two columns is about equal and, presumably, gravity does not influence the blood pressure reading. It may be concluded that the forearm should be supported at the level of the heart when determining the blood pressure with the patient in the erect postures and that the diastolic values for the blood pressure with patients in the erect postures are too high when obtained with the arm pendent.

Theoretically, the force of gravity should not affect the blood pressure reading by more than about 2 to 3 mm. of mercury when the patient's arm is moved from the pendent to the horizontal position. Lately it has been shown by one of us (Berry) that the amount of venous distention distal to the cuff of the sphygmomanometer also influences the blood pressure readings.⁵ When the patient's arm is pendent, as is the case in the usual method of taking the blood pressure when the patient stands, this factor alone increases the diastolic reading by about 8 mm. of mercury on the average (Fig. 137*a*). When the patient's forearm is supported at the level of the heart, the diastolic blood pressure reading is increased by about 4 mm. of mercury on the average, because of distention of the venous system which occurs distal to the cuff* (Fig. 137*b*). Overdistention of the venous reservoir may be largely prevented by elevating the patient's arm above shoulder level until the veins have collapsed, rapidly inflating the cuff in this position, lowering the forearm to the level of the heart with the cuff still inflated and determining the blood pressure by the technic

* The venous system distal to the cuff of the sphygmomanometer hereafter will be called the "venous reservoir."

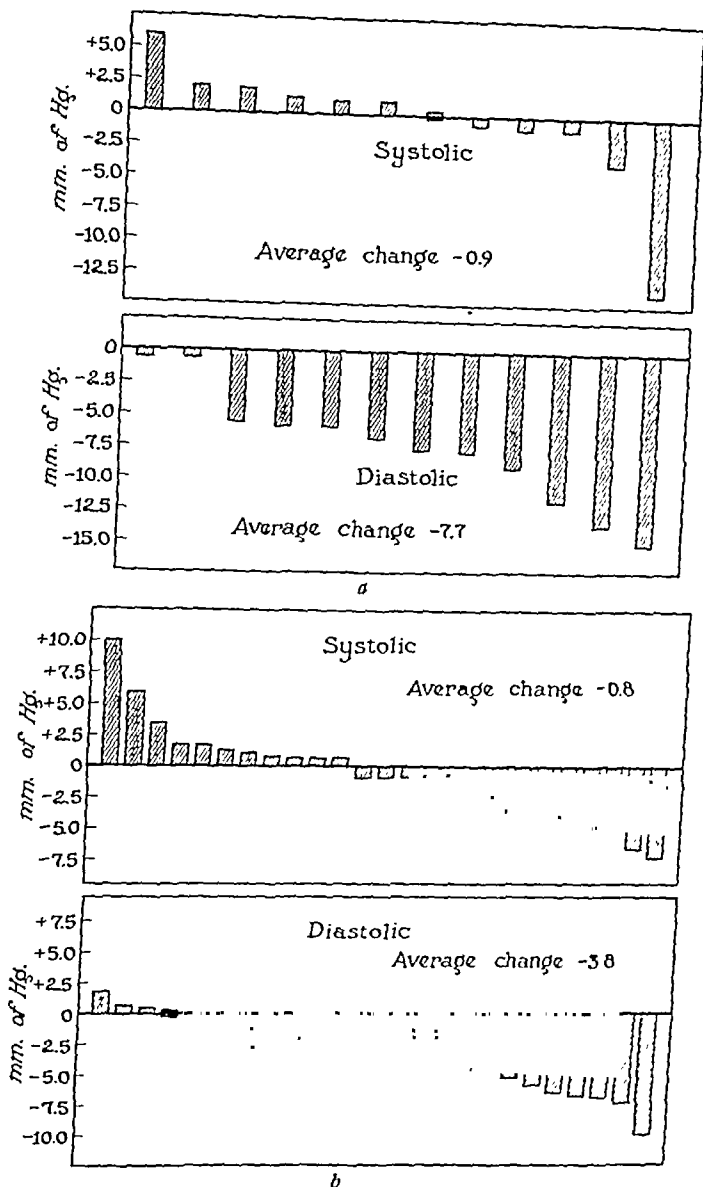


Fig. 137.—*a*, Twelve normal subjects in the passive erect posture with the arm pendent. The base lines (marked 0) in each figure indicate the average blood pressure readings in which the venous reservoir had not previously been drained. The cross-hatched columns indicate the change in the average blood pressure reading which occurred in each subject when the blood pressure was determined in the same way, except that the venous reservoir had been previously drained; *b*, twenty-five unselected subjects, standing, with the forearm supported horizontally at the level of the heart.

recommended for the sitting posture by the American Heart Association committee.*

The physician often experiences difficulty in determining the diastolic point when he attempts to record the blood pressure with the patient in the erect posture with the arm pendent;

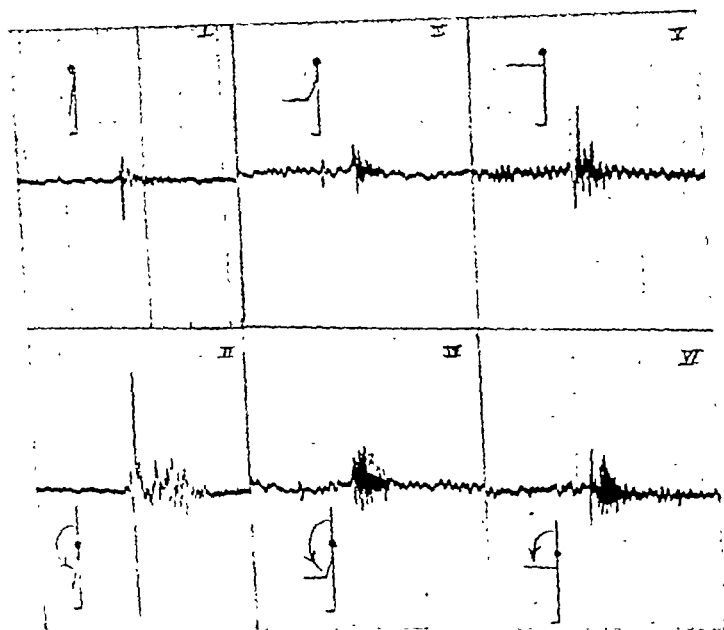


Fig. 138.—Normal subject in the standing posture. Each record shows the maximal auscultatory sound during a decompression of the cuff of the sphygmomanometer. Each record in the upper line was obtained in exactly the same manner as the record below it, except that the venous reservoir had been drained before taking the lower records. As examples, record I is a sound record of the maximal auscultatory sound with the subject's arm pendent; in record II the procedure was the same as in record I except that the venous reservoir had been previously drained in record II.

the difficulty arises because of muffling of all the auscultatory sounds or disappearance of one or more of the sound phases of Korotkoff. These phenomena are apparently the result of engorgement of the venous reservoir and may be obviated by

* This procedure hereafter will be referred to as "draining the venous reservoir."

draining the venous reservoir before determining the blood pressure. Dr. E. J. Baldes was kind enough to make sound tracings of this phenomenon in a normal subject while the subject was standing (Fig. 138). With the subject's arm pendent, draining the venous reservoir increased the loudness and duration of the auscultatory sounds remarkably. With the subject's forearm at the level of the heart, the sounds were louder at first but could still be amplified to an appreciable degree by draining the venous reservoir. With the subject's arm horizontal, the venous reservoir did not become sufficiently engorged during determination of the blood pressure to muffle the auscultatory sounds and, therefore, emptying the venous reservoir did not increase the sounds.

Roth has noted that a corset will tend to increase the blood pressure of women in the erect position, sometimes to a remarkable extent, and she has suggested that clothing which constricts the abdomen be loosened before recording the blood pressure.⁵⁸

SUMMARY AND CONCLUSIONS

In this review of postural maladaptation, we have tried to present a working picture of the complex chain of mechanisms which allow man to walk instead of to crawl; to point out that postural maladaptations may occur in the presence of a variety of diseases which may affect any link of the postural adaptation chain and account for many symptoms; to stress the diagnostic value of the simple procedure involved in comparing the blood pressure and pulse rate with the patient in the recumbent and erect postures; and finally, we propose a simple method of taking the blood pressure when the patient is erect which obviates some of the errors which occur with vascular engorgement of the arm distal to the cuff.

Sewall in 1919 stated the problem of the physician well: "In his examination of a patient the doctor is guided by his conception of the ratio of effort to use; necessity not luxury, determines his technic; the burden of a new method is intolerable unless it yields very practical results and fits easily into the routine of examination." We believe so strongly that comparison of blood pressure and pulse rates when the patient is in the erect and recumbent positions fulfills these requirements that two of us (MacLean and Horton) have advocated this

procedure as a routine part of the general physical examination at The Mayo Clinic.

We suggest the following *procedure* for recording the postural changes in blood pressure as a routine part of the physical examination:



Fig. 139.—The arm is elevated until the venous reservoir is relatively empty and the cuff is then *rapidly* inflated. The sphygmomanometer should be placed at the level of the eyes to facilitate reading.

1. After the general examination has been completed and while the results are being written, allow the patient to rest quietly for about five minutes, lying supine on the examination table.
2. While the patient is supine, record the blood pressure rapidly three to five times, depending on the amount of fluctuation between the readings, and also record the pulse rate.

3. Ask the patient to stand quietly for one minute and then take the pulse rate.

4. Elevate the patient's arm above shoulder level until the veins collapse and then rapidly inflate the cuff (Fig. 139).

5. Lower the patient's cubital fossa to the level of the heart. Clasp the subject's right hand between your right upper arm and thorax so that his forearm is horizontal at the level of the heart. Supporting the patient's elbow with the last three

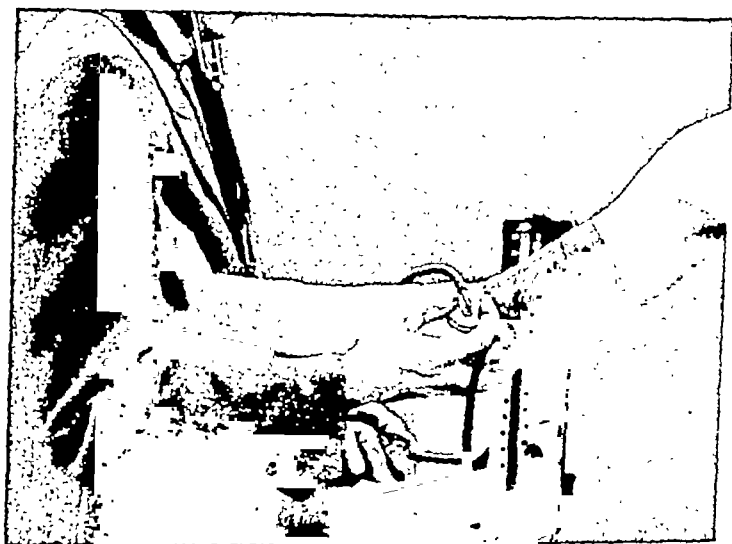


Fig. 140.—The cuff was inflated with the arm elevated. The inflation is maintained when the arm is moved to the position here shown, the stethoscope receiver is placed over the previously palpated brachial artery, and the blood pressure is determined as the cuff is deflated at the rate of 2 to 3 mm. of mercury a second.

fingers of your right hand, clasp the stethoscope in place over the brachial artery with the right thumb and forefinger and take the blood pressure in the usual way (Fig. 140).

6. In cases in which the examiner has reason to suspect latent postural maladaptation, the blood pressures and pulse rates with the patient standing should also be taken just after an exercise test.

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CRISIS TYPE PEPTIC ULCER

MORGAN W. MATTHEWS AND ANDREW B. RIVERS

The term "crisis-like" abdominal distress applies to cases in which abdominal pain is more or less sudden in its onset, is of such severity as to require the frequent administration of large doses of morphine for its relief, and is of a variable duration that ranges from a few minutes to two or even three weeks. The term, of course, has been applied to peptic ulcer because of the close resemblance that exists between certain symptoms associated with peptic ulcer and the gastric crises of *tabes dorsalis*. There are other instances in which severe, uncontrolled bouts of vomiting occur instead of the severe pain. Conditions that may give rise to these types of distress are numerous and include, among others, the colics of cholecystic and renal lithiasis, high intestinal obstruction, mesenteric thrombosis and torsion of an ovarian cyst. Although, for many years, it has been recognized that manifestations of abdominal crises occasionally occur in the course of a peptic ulcer, the condition has received but scant attention in English medical literature. Eusterman, in 1925, described five cases in which a crisis type of abdominal distress was present. However, in only one of these was pain a very prominent feature. Wilbur and Cutler, in January, 1938, reported three cases in all of which abdominal pain was the presenting complaint. Besides these two reports there are only a few scattered references in the literature that deal with this type of complaint. The condition is not so rare as the scarcity of reports would indicate for, within a period of two months, we observed eight cases in which a crisis-like type of abdominal distress was exhibited.

The association, in the same individual, of a peptic ulcer, cerebrospinal syphilis and crisis-like abdominal manifestations presents a problem in differential diagnosis that may offer extreme difficulty. It is important, however, that the cause of the

addition to the daily bouts of distress which he had learned to recognize as symptoms of ulcer, he had experienced four attacks of extremely severe abdominal pain. These attacks usually came on suddenly about two hours after a meal when he was seized with an excruciating pain in the epigastrium. This pain was so severe that on one occasion it was necessary to give him $\frac{3}{4}$ grain (0.05 gm.) of morphine sulfate and 1 grain (0.065 gm.) of codeine sulfate hypodermically, and 6 grains (0.4 gm.) of pentobarbital sodium by rectum before an appreciable amount of relief was obtained. Intractable nausea and vomiting accompanied each episode. Vomiting was so severe that it was necessary to give fluid intravenously to maintain a proper fluid balance. The duration of the attacks ranged from five days to three weeks. Hematemesis has occurred on two occasions but has never been alarming.

Roentgenologic examination of the gastro-intestinal tract had given negative results in 1930, 1931, and 1932. A duodenal ulcer had first been demonstrated roentgenologically in 1933. This finding was verified on two subsequent examinations in February and July, 1938. The remainder of the laboratory examinations gave entirely negative results.

The last attack began in the latter part of September, 1938, and was so severe that hospitalization was necessary. The patient was placed on a modified Sippy regimen. Large doses of morphine and pentobarbital sodium were required to control the distress. Two thousand cubic centimeters of fluid were supplied daily intravenously. Medical treatment for ten days was entirely without effect on the patient's symptoms.

At operation, a large duodenal ulcer on the posterior wall of the organ was found. This lesion had perforated through the posterior wall of the duodenum and formed a mass about 3 cm. in diameter. The nature of the inflammatory reaction around the duodenum prevented the use of any surgical procedure other than a posterior gastro-enterostomy. The patient's postoperative convalescence was uneventful.

COMMENT

Woltman has listed the *characteristics* of typical gastric and abdominal crises as follows: (1) sudden onset; (2) pain or vomiting, usually both, or only flatulence, extreme nausea and sialorrhea; (3) pain is usually near the midline and is symmetrical and is described as dull or sharp, aching, cramping, squeezing, gripping, burning; (4) the intensity of the pain may be mild or intense; (5) the duration of the pain varies from a few hours to a few days and is rarely continuous; (6) sudden cessation of the pain without an intercurrent abdominal complaint unless the condition is complicated by an ulcer; (7) recurrent, the intervals varying widely; (8) no tenderness on deep pressure, possibly hypersensitivity to light touch, and (9) usually associated with objective signs of syphilis.

Crohn has considered the gastric crisis of *tabes dorsalis* as

a symptom of the preataxic stage along with laryngeal, pharyngeal, rectal, vesical or renal crises and lightning-like pains in the extremities. He remarked that these manifestations may last from a few hours to a week or two. They begin and end suddenly and may be excruciatingly severe. The pain is violent, the vomiting is repeated and profuse, and the prostration is extreme; the patient has all the signs of an imminent collapse. Then, in the full height of all symptoms, the condition may resolve itself suddenly, the pain diminishes, nausea and vomiting cease, the abdominal muscles relax and the appetite returns with a rapidity that is remarkable.

Stokes⁵ has described three types of crises in *tabes dorsalis*:

(1) attacks of pain without vomiting; (2) attacks of vomiting without pain, and (3) the common type, combining both pain and vomiting. An attack usually comes on suddenly without warning. An occasional patient may have premonitory symptoms. Exhaustion, emotional stress, shock therapy, or lumbar puncture may serve as precipitating incidents. More characteristically, the attack is precipitated out of a clear sky. Pain is usually epigastric, although often it is poorly localized and ill-defined. It is of agonizing severity, grinding or spasmodic and soon reduces the average patient to convulsive sobbing and helplessness. Intense nausea may be the only symptom. Vomiting is uncontrollable and continues long after the stomach is empty. The most trying feature is the nervous collapse and disorganization that often ensues during the several days to a week or more that the attack may last. The recovery is almost as striking as the onset. The pain and vomiting disappear within a few hours and the pale, exhausted patient rapidly regains composure and appetite. The most outstanding symptom characteristic of the majority of gastric and other visceral crises in cases of *tabes* is the periodicity which sometimes is as perfect as that of the menstrual function and cyclic vomiting. The attacks tend to follow closer and closer on one another in the lapse of months or years, so that the patient ultimately can no longer regain his physical equilibrium between them. Cases have been reported in which attacks of belching of explosive amounts of gas were the only signs of a crisis. These gaseous crises are not necessarily accompanied by nausea and vomiting. The vivid descriptions of the gastric crises of *tabes* by these

three authors correspond in many features to the attacks experienced by our patients. On the basis of the attack itself, there is little difference, if any, between the gastric crisis that is due to tabes dorsalis and the crisis-like pain of peptic ulcer. There are two types of crisis-like ulcer syndromes and both of them usually are indicative of a complicated lesion. The first is that in which nausea and vomiting are the predominant symptoms; in the other, severe pain is of greatest importance. The latter is by far the more frequent. Those ulcers which are accompanied by exacerbations of nausea and vomiting lasting for from a few days to several weeks usually can be demonstrated to be associated with some degree of pyloric obstruction or may be found to be productive of an unusually active pylorospasm. The crisis type of ulcer syndrome characterized by severe intractable pain is almost invariably caused by deep penetration of the causative lesion with invasion of the tissues contiguous with the stomach or intestine. Although at times difficult, a differentiation can be made between the crisis type of pain due to penetration of an ulcer and the gastric crisis of syphilis of the central nervous system.

There are certain *features* in cases of crisis-like pain due to peptic ulcer that should *make one suspicious of the presence of a peptic ulcer*: (1) The time of onset of the pain, although frequently irregular, often retains certain characteristics of the pain that accompanies ulcer. There is a tendency for the pain to occur in direct relationship to meals. Most commonly, the onset of the pain begins one-half to three hours after the ingestion of food. Not infrequently, the distress may occur around midnight or at 1 o'clock in the morning. Occasionally, night pain is the only symptom. (2) Although the effect of food and soda on the pain is inconstant, in most cases their ingestion will relieve the symptoms to an appreciable degree. Even though the distress is incompletely relieved by food or alkali, the fact that diminution of distress was attainable in this way should make one suspicious of the presence of a peptic ulcer. Nothing whatsoever has any influence on the seizure of a gastric crisis due to tabes except large doses of opiates. (3) Hemorrhage during the course of a gastric crisis due to tabes dorsalis, although it does occasionally occur, is quite rare. Crohn has stated: "Vomiting of blood during a crisis is a rare complica-

tion, only about thirty instances being reported." Later he stated: "Every case of crises in which hemorrhage takes place should be strongly suspected of an independent lesion." The response to treatment will occasionally enable a differential diagnosis to be made. In cases in which the crisis-like pain is due to peptic ulcer, frequently benefit will be derived from alkalis and large doses of barbiturates. We employ $1\frac{1}{2}$ grain (0.1 gm.) of pentobarbital sodium every two to four hours. However, these drugs appear to have no effect on the course of a gastric crisis due to *tabes dorsalis*.

The *previous history* of the case may be the most important single factor in making a distinction between the two conditions. In most instances, persons who have a peptic ulcer, on careful questioning, relate a history suggestive of such a lesion. In any case in which is presented a history of periodic recurrence of an intermittent type of gastric distress that occurs at variable intervals after meals and that is relieved by food and alkali, a peptic ulcer should be suspected of being present, no matter how bizarre the additional symptomatology may be. A history of night pain occurring at about midnight or at 1 o'clock in the morning, severe enough to awaken the patient from a sound sleep may be an important lead in the diagnosis of peptic ulcer, although the diurnal symptoms are atypical. The history of the occurrence of frank hematemesis or melena associated with any indigestion should make one think immediately of a lesion in the stomach or duodenum.

The *physical examination* will frequently be of great aid in distinguishing between the two conditions. The finding of definite neurologic signs such as fixed or irregular pupils and absent deep reflexes at once throws the weight of the evidence in favor of a diagnosis of *tabes dorsalis*. Woltman has expressed the belief that in the majority of cases of abdominal crisis due to *tabes dorsalis*, involvement of the central nervous system is well advanced and definite neurologic manifestations of the disease can be found. Argyll Robertson pupils and absent deep reflexes are the most common findings. Other manifestations include involvement of the other cranial nerves, especially those governing the movements of the eyes and eyelids. Stasis of the upper lid, paralysis of the lateral rectus which causes an internal strabismus, and optic atrophy are

the more frequent signs. Absence of vibratory sensation, especially in the lower extremities, is also common. In a case in which the predominant abdominal complaints are nausea or vomiting with or without pain, the discovery of such findings should lead to a suspicion of the presence of tabes dorsalis.

Invaluable aid is frequently obtained from *examinations* of the *blood* and *spinal fluid*. It should be pointed out that in 32 per cent of cases of tabes dorsalis, serologic examination of the blood will give negative results. Hence, it is obvious that the use of a blood test in an effort to confirm the clinical impression of tabes dorsalis will result in an incorrect diagnosis in a third of the cases. Examination of the spinal fluid is a much more valuable diagnostic aid. In only 5 per cent of patients who have clinical signs of tabes, without a history of previous treatment for syphilis, will the serologic examination of the spinal fluid give negative results. Stokes⁵ has placed emphasis on the signs of tabes dorsalis elicited by the history and examination, rather than on the reaction of the blood and spinal fluid.

Roentgenologic examination of the gastro-intestinal tract is frequently an invaluable diagnostic procedure and in the majority of cases of peptic ulcer in the stomach or duodenum such a procedure will give evidence of such a lesion. In a small percentage of cases, the lesion cannot be demonstrated by this method. Most of the lesions which remain undemonstrable during roentgenologic investigations are situated on the posterior wall of the stomach or duodenum, or high on the lesser curvature of the stomach. Therefore, failure to demonstrate an ulcer by roentgenologic means cannot be construed to mean that an ulcer does not exist.

By the evaluation of data obtainable from the history, laboratory investigations usually enable a differential diagnosis to be made between the crisis type of distress caused by peptic ulcer and that caused by tabes dorsalis. In a certain number of cases, however, *both* tabes dorsalis and peptic ulcer *coexist* in the same individual. The problem of differential diagnosis in these cases is indeed difficult. Hunt and Lisa reported the postmortem findings in four cases in which such an association was observed. They believed that the condition is an uncommon one but that it occurs more frequently than is gen-

erally suspected, the peptic ulcer being unrecognized. They concluded that such ulcers are not trophic disturbances similar to those seen in cases of chronic leg ulcer (gummas), but are independent lesions. Crohn has stated: "In a case which shows predominant abdominal complaints, such as pain and vomiting, the discovery of an Argyll Robertson pupil or absent deep reflexes will tend ordinarily to the ready diagnosis of tabes with gastric crises, and undoubtedly correctly so. It is essential in every such case that we investigate thoroughly the possibility of a coexistent organic abdominal lesion. Such a distinction is usually made with considerable difficulty, for the complexity of the symptoms often defies solution; even with all the laboratory data that can be amassed at our right hand we remain not infrequently undecided." Crohn pointed out that in the majority of cases of gastric crisis of syphilitic origin, primarily the diagnosis of peptic ulcer is made and treatment is given for this condition and the discovery of a positive Wassermann reaction or physical signs of tabes often swings the diagnosis to tabes dorsalis and allows the diagnosis of ulcer to lapse. In his report, he included a case of a penetrating peptic ulcer and fully developed tabes dorsalis.

Even among patients who have coexistent peptic ulcer and tabes dorsalis, it is usually possible, by careful evaluation of symptoms, to determine which disease is responsible for the presenting difficulty. It is well to remember that although syphilis may mimic most diseases, it almost never produces symptoms suggestive of uncomplicated peptic ulcer. If, therefore, the two diseases coexist and if the symptoms possess any suggestion of ulcer or of its complications such as bleeding, penetration or obstruction, it is well to assume that the ulcer may be the offending lesion.

There must be many cases similar to the one reported by Askey. His patient suffered from recurrent episodes of epigastric pain, nausea and vomiting severe enough to require the administration of morphine. Tabes dorsalis had been present for ten years. The attacks lasted for "a few days" and were followed by normal health. The author saw the patient in one attack and made a diagnosis of perforating peptic ulcer. Operation confirmed this opinion. Four and a half years later, the patient had another bout of his distress and it was con-

sidered to be due to *tabes dorsalis*. The existence of a second perforation was not recognized until four days later. Necropsy revealed a perforating peptic ulcer of the pylorus.

SUMMARY

Two cases have been presented in order to draw attention to the fact that some patients who have *tabes dorsalis* with a crisis type of abdominal pain, nausea and vomiting, have in addition to cerebrospinal syphilis, a peptic ulcer. This latter lesion may be the cause of the presenting complaint and every effort should be made to determine, if possible, which of the two existent conditions is responsible for the malady.

Crisis types of peptic ulcers are usually complicated lesions. If severe pain unamenable to the usual methods of relieving the distress of ulcer is the predominant symptom, the lesion is of the penetrating type. If intractable bouts of vomiting are present, the ulcer usually interferes directly or indirectly with pyloric function. In either case, the condition is best handled surgically.

Patients who have tabetic gastric crises should be given the benefit of roentgenologic investigation of the upper portion of the gastro-intestinal tract. Not infrequently, some lesions that involve the stomach or duodenum will be demonstrated by such a procedure.

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SERUM AMYLASE AND SERUM LIPASE IN THE DIAGNOSIS OF DISEASE OF THE PANCREAS

MANDRED W. COMFORT AND ARNOLD E. OSTERBERG

The recognition of pancreatitis is one of the most difficult diagnostic problems confronting the internist. This is not surprising when one considers that the pancreas is situated deep in the abdomen, that a competent test for the detection of disturbances of its functions has not been used widely, and that disease of the pancreas mimics disease of the surrounding organs. It is true that persistent pain or pain of great severity refractory to relief with morphine, and pain and tenderness in the left upper quadrant of the abdomen, strongly suggest pancreatic inflammation, but these clinical features do not occur frequently enough in the course of acute or chronic pancreatitis to overcome the anatomic and clinical barriers lying in the way of accurate diagnosis. Tests of function of the islands of Langerhans, long available for the diagnosis of pancreatitis, are probably used too infrequently during the acute attacks but they possess the disadvantage that when positive, it is often impossible to decide whether the dysfunction of the islet tissue preceded or was the result of the attack. Frequent recognition of acute pancreatitis has awaited the development and widespread clinical use of a test for disturbance of pancreatic function other than that of the internal secretion of the islands of Langerhans. In the determination of values for enzymes in the serum, we believe a test answering the demand in a satisfactory manner has been found. We are confident that the estimation of the values for enzymes in the serum is invaluable not only in the diagnosis of acute pancreatitis from any cause but also in the diagnosis of chronic pancreatitis so long as the process is active and functioning acinar tissue exists and in the diagnosis of malignant disease of the pancreas.

EXPERIMENTAL DATA ON THE ORIGIN AND FATE OF ENZYMES
IN THE SERUM

A review of the experimental data discloses that the use of enzymatic values of the serum in the diagnosis of pancreatic disease is founded on well established facts. Amylase and probably lipase are constantly present in small amounts in the blood stream; both the amylolytic and lipolytic activity are relatively constant in healthy individuals. The activity of these enzymes may vary considerably in different persons and seems to be unaffected by starvation or by foods of various types. Amylase and lipase of the serum both originate, at least partly, in the pancreas. Several reasons for this belief can be advanced: First, experimental pancreatectomy done on animals has been followed with few exceptions by temporarily decreased values for serum amylase. Second, ligation of the pancreatic ducts of animals always has been followed within a few hours by a rapid rise in values for both serum amylase and lipase. These values gradually returned to normal in eight to fifteen days. Third, in pancreatitis induced experimentally by the injection of bile into the pancreatic ducts of animals there has been a marked increase in the concentration of amylase and lipase in the serum; maximal values have been registered within a very few hours and the return to normal usually has occurred within the first seven to ten days, even though pathologic changes persisted in the pancreas. Amylase in the serum also may possibly arise in the salivary glands. Both amylase and lipase are possibly absorbed directly into the blood stream from the pancreas in health while in the presence of experimental or clinical obstruction to the pancreatic ducts and in the presence of pancreatitis it is presumed that the rupture of small pancreatic canaliculi occurs, permitting entrance of pancreatic juice into the blood stream through the lymph vessels. The factors regulating concentration of amylase and lipase in the serum of healthy persons are not well understood. It may be assumed that the pituitary body and thyroid gland exert some influence inasmuch as removal of the pituitary body of dogs is followed by a twofold increase of amylase in the serum, and hyperthyroidism is accompanied by decrease in the amount of amylase in the serum. Both amylase and lipase are excreted through the kidneys, and the urine

probably serves as a vehicle for elimination of excessive amounts of both enzymes.

CHEMICAL METHODS

Lipase.—The following method is used at the Clinic for determination of the concentration of lipase in the serum: To 1 c.c. of serum is added 3 c.c. of water and 0.5 c.c. of Clark's buffer "pH 7" and 2 c.c. of olive oil emulsion (List No. 8100 Abbott Laboratories). These are mixed and incubated for twenty-four hours at 38° C. The mixture is shaken several times during incubation. Three cubic centimeters of 95 per cent alcohol is then added to break the emulsion and the material is titrated with a twentieth-normal solution of sodium hydroxide by using phenolphthalein as an indicator. The results are interpreted in cubic centimeters of twentieth-normal solution of sodium hydroxide. A blank should be run at the same time as follows: Three cubic centimeters of water is added to 1 c.c. of serum and the mixture is heated at 70° C. for about five minutes; then the buffer and substrate are added and the mixture is incubated and titrated as described previously. The blank value for the titration is subtracted from that for the unknown and the values are expressed in cubic centimeters of twentieth-normal solution of sodium hydroxide per 1 c.c. of serum.

Amylase.—The method for determining the concentration of amylase in the serum is as follows: To 0.5 c.c. of blood serum is added 2.0 c.c. of starch solution (1.5 mg. starch in 2 c.c. of 0.25 per cent solution of sodium chloride); the mixture is incubated at 40° C. for five minutes. Half a cubic centimeter of the incubated solution is added to 0.5 c.c. of 0.002 N solution of iodine in a 2 per cent solution of potassium iodide. If the mixture is blue, it should be incubated another five minutes and retested with the solution of iodine. The end point is a pure brown color or absence of blue. If a high content of amylase is present, one should use less serum and reincubate the diluted solution (diluent, 0.9 per cent solution of sodium chloride). The calculation is made as follows:

$$\frac{1600 \text{ (starch factor)}}{\text{minutes required to reach end point}} = \text{units of amylase.}$$

VALUES FOR ENZYMES IN THE SERUM

Of patients without known abdominal disease.—The range of values for *lipase* is 0–1.5 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum; for *amylase* the range is up to 320 units in the serum of patients without known abdominal disease.

In cases of *pancreatitis*.—With the development of acute pancreatitis, the values for serum enzyme rapidly rise above the normal range. The values for serum *lipase* have reached 12 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum and the value for serum *amylase* has reached 1600 units. This behavior of the serum enzymes is well illustrated in the following case.

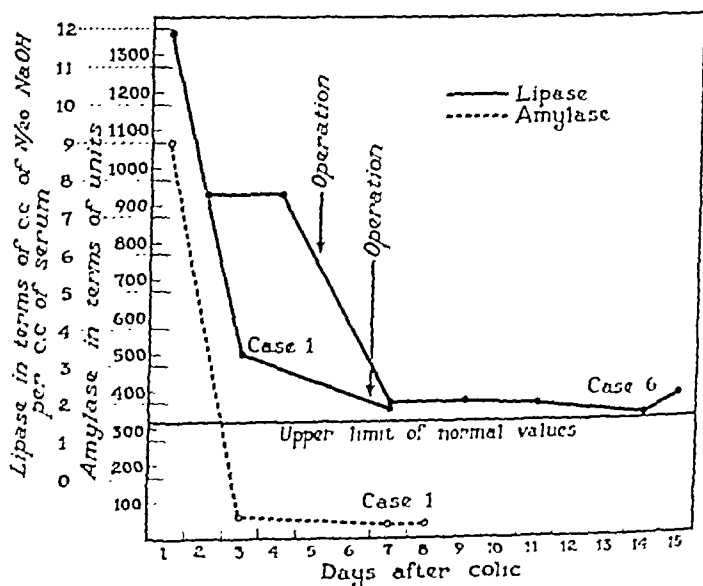


Fig. 141.—Curves showing behavior of values for serum lipase and serum amylase in case of acute pancreatitis associated with subacute cholecystitis (case 1) and in case of acute pancreatitis secondary to perforating duodenal ulcer (case 6).

Case I.—A woman, aged fifty-five years, registered at the Clinic February 17, 1938. She had had gaseous indigestion since 1933. On February 9, nausea, anorexia and bloating had been noted. Three days later pain had developed

in the right upper quadrant of the abdomen. The pain had extended to the back. On the next day jaundice had appeared. Attacks of pain had occurred daily since the onset of the illness. Examination revealed a moderate degree of jaundice and rather marked tenderness across the epigastrium, probably more marked in the right upper quadrant of the abdomen. The leukocyte count was normal, the concentration of bilirubin in the serum was 6.8 mg. per 100 c.c. and the van den Bergh reaction was direct.

The clinical diagnosis was subacute cholecystitis with gallstones, and a stone in the common bile duct. The continuous character of the pain and the tenderness in the left as well as the right upper quadrant of the abdomen suggested associated pancreatitis. On February 19, determinations of the values for the enzymes in the serum showed the value for lipase to be 11.9 c.c. of twentieth-normal solution of sodium hydroxide and that for amylase to be 1060 units (Fig. 141). These high values confirmed the clinical impression of pancreatitis. On February 24, exploratory laparotomy confirmed the clinical diagnosis. The entire pancreas was thickened from head to tail and was firm in consistency.

The behavior of the enzymatic values during convalescence from an acute episode in Case I is illustrated in Fig. 141. As in this case, the values fall very promptly and usually reach normal within ten to fourteen days. The values for amylase often return to normal much more quickly than do the values for lipase. In those cases in which the clinical symptoms such as pain, fever, leukocytosis and local tenderness persist, indicating that the process is active, the values may remain high for three weeks or longer. It is to be emphasized, however, that determinations must usually be carried out within a relatively short period of time after the attack if elevated values are to be obtained.

Increased values may persist for many months when the inflammation becomes chronic but remains active. This is well illustrated in the following case:

Case II.—A youth, aged eighteen years, registered at the Clinic December 13, 1938. He had been well until eighteen months previously when he first noted constant soreness in the epigastrium and fullness after meals. Twelve months before his registration he had experienced his first attack of epigastric pain; this had required morphine for relief. Four other severe attacks, as well as many minor attacks, had occurred up to September, 1938. Since that time three or four minor attacks had occurred each week. Steatorrhea had developed.

Physical examination was essentially negative with the exception of slight tenderness in the epigastrium, some enlargement of the liver, a palpable spleen

and a slight degree of jaundice. The significant laboratory findings were a concentration of 6.8 mg. of bilirubin per 100 c.c. of serum, positive glucose tolerance test, a lipase value of 3.3 c.c. and an amylase value of 530 units. The diagnosis was chronic pancreatitis with hepatitis and splenomegaly. Exploratory laparotomy, which was performed May 12, 1939, confirmed the clinical diagnosis. The pancreas was markedly diseased and the spleen was three or four times normal size. Biopsy of the liver showed hepatitis.

On January 17, January 27, May 3, May 17, May 30 and October 3, 1939, the values for the serum lipase were 3.3 c.c., 4.4 c.c., 2.0 c.c., 0.5 c.c., 0.6 c.c. and 2.0 c.c., respectively, and those for the serum amylase were 530, 160, 110, less than 50, 120 and 80 units, respectively. The value for the lipase was consistently elevated, except immediately postoperatively, but that for the serum amylase was elevated only in January, 1939. This illustrates not only the long continued elevation of values for serum enzymes in cases of chronic pancreatitis in which the process is active but also again shows the lack of parallelism between values for serum lipase and serum amylase and of the tendency for the values for the amylase to return to normal before the values for lipase do so.

In cases of carcinoma of the pancreas.—The determination of concentration of enzymes in the serum has been valuable in cases of malignant as well as benign disease of the pancreas. The assistance rendered to the clinician in malignant disease of the pancreas is well illustrated in the following case:

Case III.—A man, aged fifty-four years, registered at the Clinic on September 26, 1938. Six months previously a severe boring pain had developed in the region of the umbilicus. The pain had extended to the back and had been worse at night; nothing had been found that would give complete relief. For six weeks before the patient came to the Clinic the pain had been much worse than it had been previously. He had lost 35 pounds (15.9 kg.). Slight jaundice was present; the liver was enlarged but the abdomen was so obese that it was impossible to be certain that the gallbladder was palpable. The concentration of bilirubin in the serum was 7.5 mg. per 100 c.c. and the van den Bergh reaction was direct. Duodenal drainage produced a small amount of bile. The lipolytic activity of the serum in terms of cubic centimeters of twentieth-normal solution of sodium hydroxide was 3.5. The value for the serum amylase was 533 units (Fig. 142). Although the character of the pain, and the progression of the symptoms strongly favored a diagnosis of carcinoma of the head of the pancreas, partial patency of the common bile duct, as indicated by the presence of bile in the duodenum, and the inability to palpate the gallbladder left reasonable doubt regarding the nature of the disease. Definitely increased values for serum lipase and serum amylase indicated that the disease was definitely in the pancreas. The clinical diagnosis of carcinoma of the head of the pancreas was confirmed by exploratory laparotomy. The surgeon reported that the pancreas was markedly indurated and nodular, par-

ticularly in the region of the head. A palliative cholecystoduodenostomy was performed. The patient was dismissed from our care, October 24, 1938, and

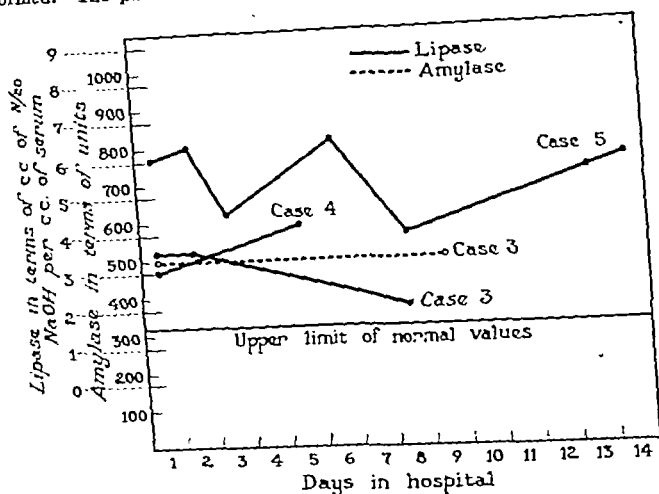


Fig. 142.—Curves showing behavior of values for serum amylase and serum lipase in case of carcinoma of the head of the pancreas (case 3), in case of carcinoma of the body of the pancreas (case 4) and in case of carcinoma of the ampulla of Vater (case 5).

died at home March 16, 1939. At the time of his death definite abdominal carcinomatosis was present.

The finding of increased values for enzymes in serum in cases of malignant obstructive jaundice is good confirmatory evidence that the pancreas is involved in the pathologic process. It is particularly acceptable evidence when the gall-bladder cannot be palpated because of a muscular or fat abdominal wall.

Elevated values for enzymes in the serum occur in an occasional case of carcinoma of the pancreas in which the body and tail of the organ are chiefly involved. In such cases elevated values are of greater importance than they are in cases in which the carcinoma involves the head of the pancreas, since obstructive jaundice and palpable gallbladder (findings on which the diagnosis of carcinoma of the head of the pancreas can be made without these laboratory investigations) are absent when carcinoma of the pancreas involves only the body and the tail. This is well illustrated by the following case:

Case IV.—A man, aged sixty-three years, registered at the Clinic March 3, 1937. He had complained of gaseous dyspepsia for two years but only in the past four weeks had he experienced any discomfort in the upper part of the abdomen. At that time diffuse discomfort had developed in the upper part of the abdomen. The discomfort had occurred about two hours after meals and had not been relieved by taking food and bicarbonate of soda. The results of general physical examination were essentially negative; the significant laboratory findings were those of secondary anemia; the sedimentation rate was 46 mm. at the end of one hour. The concentration of bilirubin was within normal limits. Roentgenologic examination of the stomach showed a deformity of the duodenum, which was suggestive of ulcer, as well as marked hypertrophy of the gastric rugae with localized hypertrophic gastritis on the posterior wall of the upper portion of the stomach. Following the administration of a test meal, 90 c.c. of gastric contents were obtained. Analysis of the contents by the method of Töpfer disclosed the following values: total acidity 64 and free hydrochloric acid 52. Gastroscopy revealed marked hypertrophy of the gastric mucosa.

The roentgenologic and gastroscopic findings at first appeared to explain the cause of the symptoms, but the age of the patient, the marked anemia and the apparently progressive course of the disease aroused the suspicion of something other than the duodenal ulcer as a cause of the symptoms. The pancreas was suspected and the value for serum lipase was determined; this was found to be 3 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum (Fig. 142). This finding indicated that the pancreas was involved. It was concluded that the deformity of the duodenum and the gastritis were not primary but were secondary to pancreatic disease. The clinical diagnosis was carcinoma of the pancreas. Exploratory laparotomy revealed a large mass which arose from the body of the pancreas and pushed the stomach anteriorly. There were many enlarged lymph nodes; microscopic examination of one of the enlarged lymph nodes revealed adenocarcinoma, grade 4.

A recent review of data in cases of carcinoma of the pancreas in which the values for serum lipase and serum amylase were determined showed that the value for the lipase was elevated in twenty-eight, or 40.5 per cent, of sixty-nine cases of carcinoma of the pancreas and that the value for the amylase was elevated in only two, or 8 per cent, of twenty-four cases of carcinoma of the pancreas. In cases of malignant disease of the pancreas, much more information apparently is to be expected from the determination of the value for serum lipase than from the determination of the value of serum amylase.

Increased concentrations of enzymes in serum are likewise of value in pointing out pancreatic involvement in carcinomatous lesions of the ampulla of Vater.

Case V.—A woman, aged forty-eight years, registered at the Clinic on September 9, 1933. She had felt perfectly well until February, 1932, when she had had a mild attack of abdominal pain with jaundice. This attack had ceased but another attack had occurred in October, 1932. At that time there had been deep jaundice, chills, fever, and considerable pain, particularly in the epigastrium. All of the symptoms had disappeared by January, 1933. In June, 1933, there had been another episode of jaundice and the pain had occurred intermittently since that time. The jaundice had fluctuated, the temperature had varied between 100° and 103° F. (38° and 40° C.), and a persistent leukocytosis had been present. The concentration of bilirubin was 15 mg. per 100 c.c. of serum when the patient was first seen at the Clinic but it gradually declined to 10 mg. per 100 c.c. on the twenty-first of September. The van den Bergh reaction was direct. The value for serum lipase fluctuated between 6.3 and 3.9 c.c. of twentieth-normal solution of sodium hydroxide (Fig. 142). Duodenal drainage produced a small amount of bile.

The diagnosis was intermittent obstruction of the common bile duct, jaundice and pancreatitis. Exploratory laparotomy on September 22 revealed an indurated mass 5 cm. in diameter at the head of the pancreas. Multiple small carcinomatous metastases were seen in the liver; the gallbladder was distended but its walls were normal in color and thickness. The patient died September 23. Necropsy revealed carcinoma of the ampulla of Vater.

In this case the history and the symptoms clearly pointed to an obstructive lesion of the common bile duct and cholangitis. The elevated values for serum lipase pointed to pancreatic involvement. Elevated values for serum enzymes do not distinguish benign lesions from malignant lesions of the pancreas; they do, however, definitely point to disease of the pancreas. The values for lipase have been elevated in six, or 67 per cent, of nine cases of carcinoma of the ampulla of Vater, but the concentration of amylase in the serum has not been elevated in four cases of carcinoma of the ampulla of Vater in which the concentration has been determined.

If circumstances permit continued observation of the patient, the type of curve constructed from repeated determinations of the concentration of amylase and lipase in the serum may give some indication of the nature of the underlying process. In cases of carcinoma of the head of the pancreas the values for serum enzymes tend to remain elevated and sometimes form an almost flat curve (Fig. 142). This is in contrast with the rapid fall toward normal levels which occurs with the subsidence of an acute inflammation of the pancreas (Fig. 141, Cases I and VI). The tendency of the values for enzymes to remain elevated in cases of carcinoma of the pancreas, even

after cholecystogastrostomy, is probably the result of the chronic, persistent obstruction of the pancreatic duct, whereas the rapid rise and fall which appear during the course of acute pancreatic inflammation may be accounted for by the transitory nature of the inflammation and the obstruction. Occasionally, however, the behavior of the enzymes in the serum in cases of carcinoma of the pancreas resembles greatly that seen in cases of pancreatitis and in these instances the fluctuations may point either to a transitory inflammation of the pancreas or to intermittency of the obstruction.

In cases of carcinoma of the biliary tract.—It is important to know whether elevated values for the enzymes in the serum occur in cases of malignant disease of the biliary tract, a condition which closely simulates carcinoma of the head of the pancreas. Normal values for serum lipase have been obtained in twenty-three cases of malignant disease involving the common bile duct, the hepatic ducts or gallbladder, and an elevated value has been obtained in only one case of carcinoma of the hepatic duct. Similarly, normal values for serum amylase have been found in seven cases of carcinoma of the common bile duct and of the hepatic duct and gallbladder, and elevated values have not been noted in similar cases. Post-mortem confirmation of the site of the carcinoma in the hepatic duct in the one case in which the concentration of serum lipase was elevated was not obtained, and because normal values are almost universally absent in cases of malignant disease of the biliary tract, the elevated values in this particular case must be accepted with some reservation. The almost universal occurrence of normal values in malignant disease of the biliary tract without involvement of the pancreas is particularly significant since elevated values in cases of malignant obstructive jaundice usually indicate that the lesion does not involve the gallbladder, common bile duct and hepatic duct, but denote that it involves the pancreas.

VALUES FOR SERUM ENZYMES IN OTHER CONDITIONS

Peptic ulcer.—Values for serum lipase have been determined in three cases of gastric ulcer, 102 cases of duodenal ulcer and nine cases of gastritis, and values for serum amylase have been obtained in three cases of gastric ulcer, twenty-two

cases of duodenal ulcer and six cases of gastritis. Elevated values for serum lipase have been obtained in one case of gastric ulcer and six cases of duodenal ulcer, and elevated values for amylase have been obtained in one case of gastric ulcer. In every case in which elevated values for both enzymes were obtained the peptic ulcer had perforated into the pancreas and had produced secondary pancreatitis. The following case illustrates in a striking fashion the occurrence of elevated values in pancreatitis due to a perforated ulcer:

Case VI.—A man, aged fifty years, registered at the Clinic, June 12, 1935. For many years he had been in the custom of arising at 4 a.m. because of abdominal distress and the desire for defecation. He customarily had eaten breakfast at this time but was not certain that he had done this for relief of the distress. In March, 1935, he had noted intrascapular pain which extended into the epigastrium and was relieved by vomiting. On June 5 he had had a severe attack of pain in the upper part of the abdomen. Morphine had been required for relief and the pain had been followed by jaundice. He thought that a lump had been present in the epigastrium since the last attack.

Examination revealed a moderate degree of jaundice, some tenderness and rigidity in the right upper quadrant of the abdomen, slight secondary anemia, a concentration of bilirubin of 6.8 mg. per 100 c.c. of serum and a direct van den Bergh reaction. The concentration of serum lipase was 7.6 c.c. of twentieth-normal solution of sodium hydroxide for each cubic centimeter of serum. The clinical diagnosis was acute pancreatitis, probably secondary to acute cholecystitis. Exploratory laparotomy revealed a huge tumor of the head of the pancreas, which formed a mass 7.5 cm. in diameter. While the mass had more of the brawny induration of pancreatitis than the stony hard irregular feeling of carcinoma, its exact nature was indefinite. Moreover, the gallbladder and common bile duct were distended, as in cases of carcinomatous obstruction. Cholecystogastrostomy was performed.

The patient continued to have mild attacks of epigastric distress and returned in August, 1938, with symptoms of gastric retention. Roentgenologic examination showed considerable secondary dilatation of the stomach and deformity of the duodenum together with definite obstruction of the duodenum. On August 11, a posterior gastro-enterostomy was performed for duodenal obstruction. The pancreas was normal in size and there was no evidence of malignancy. Two months after the operation the typical symptoms of ulcer developed and the pain shifted to the left and into the lower part of the abdomen, as is typically seen in cases of gastrojejunal ulcer. Roentgenologic examination of the stomach in October, 1939, showed the former duodenal deformity and, in addition, a gastrojejunal ulcer with associated gastrojejunitis.

In retrospect, it is clear that the patient was suffering from duodenal ulcer and that the mass in the head of the pancreas was due to inflammation secondary to perforation of the

duodenal ulcer. The behavior of the concentration of the lipase in the serum (Fig. 141) correctly pointed to pancreatic inflammation.

Hepatic disease.—Values for serum lipase have been determined in thirty-two cases of *cirrhosis* and thirty-one cases of *hepatitis*. Elevated values have been obtained in four cases of cirrhosis and four cases of hepatitis. The diagnoses in these eight cases were, respectively, hepatitis with jaundice due to Malta fever, hepatitis with jaundice due to lobar pneumonia, toxic hepatitis due to cinchophen poisoning, toxic hepatitis of unknown cause, biliary cirrhosis in two cases and portal cirrhosis in two cases. The values for the serum lipase in these eight cases were, respectively, 2.7, 3.5, 1.6, 1.8, 1.6, 1.8, 2.0, and 2.4 c.c. of twentieth-normal solution of sodium hydroxide per cubic centimeter of serum. In none of these cases did the slightly elevated values obscure the diagnoses. The high values obtained in the case of Malta fever and in the case of pneumonia were not of diagnostic interest. We believe that elevated values in hepatic disease usually are due to associated pancreatitis. Elevated values may possibly prove to be a source of confusion to the clinician but here, as elsewhere, laboratory tests must be interpreted in the light of the accompanying clinical picture.

Values for serum amylase have been determined in ten cases of cirrhosis and twelve cases of hepatitis. The values have been normal in these twenty-two cases.

Carcinoma of the stomach.—Malignant disease of itself does not produce elevated values of serum lipase and serum amylase. However, elevated values have been found in two of thirty-one cases of carcinoma of the stomach in which values for serum lipase have been determined. In each of these cases, the carcinoma had penetrated into and involved the pancreas. Elevation of values for serum amylase did not occur in three cases of carcinoma of the stomach in which the values were determined.

SUMMARY

Determinations of the concentration of serum lipase and serum amylase are highly efficient means of detecting disease of the pancreas, but elevated values do not indicate the type

of pancreatic disease present. The differential diagnosis of the type of pancreatic disease must be made on the basis of the history and clinical findings. In some instances, if the opportunity for long-continued observation is possible, the type of plotted curve which can be drawn from the values for the enzymes in the serum may indicate the type of pancreatic disease present. Elevated values for serum lipase in hepatic disease may sometimes cause confusion in making a diagnosis, but if the elevation in the value for this enzyme is always interpreted in the light of historical and clinical findings, this will seldom be the case. At the present time the determination of the value for serum lipase as a test of pancreatic disease appears to be more reliable than does the determination of the value for serum amylase.

SIGNIFICANCE OF RETINAL CHANGES IN THE TOXEMIAS OF PREGNANCY

ROBERT D. MUSSEY

The existence of visible changes in the retinal vessels of women suffering from the acute late toxemias of pregnancy has been appreciated for a number of years, and the importance of the ophthalmoscopic examination in the diagnosis and management of the toxic hypertensive syndrome has been repeatedly stressed. Schiötz, Cheney, Mylius, Friedenwald, Hallum^{12, 13} and Wagener have reported alterations in previously normal retinal vessels in the course of late toxemias of pregnancy.

Stander and Peckham²³ have independently arrived at the statement that about 10 per cent of pregnant women in this country present some evidence of late toxemia, such as hypertension, edema and albuminuria. Although this figure may vary with locality and living conditions, nevertheless it is an indication that every physician must be alert to detect this not uncommon pathologic state.

For purposes of clarity, the compromise classification of the toxemias which has been agreed on by a subcommittee of The American Committee on Maternal Welfare will be used. This divides the toxemias of pregnancy, with which this paper is concerned, into four groups: (1) *hypertensive disease* (pre-existing), (2) *renal disease* (pre-existing), (3) *preeclampsia*, and (4) *eclampsia*, thus distinguishing those conditions present before the establishment of pregnancy and those which arise in the course of pregnancy. Later these headings will be referred to in relation to retinal examination.

It is generally agreed that the visible changes in the retinal vessels in the late toxemias are only one of several pathologic and clinical signs pointing to widespread vascular damage affecting the arterioles and precapillary vessels. In vessels of

the *nail fold*, alternate dilatation and contraction on the basis of spasm, together with elongation of the capillary loops and more or less stasis, have been described in preeclamptic and eclamptic patients by Linzemeier, Baer and Reis, and Hinselmann, Nettekoven and Silberbach. Similar changes have been noted in biopsy material obtained from the pectoral muscles of nonpregnant patients with vascular disease and glomerulonephritis and also of a small number of patients with preeclamptic toxemia just prior to delivery.

Glomerular alterations have also been observed in cases of preeclampsia which came to necropsy and are considered by some to be related to the pathologic changes associated with glomerulonephritis of infectious origin. Bell, however, expressed the opinion that the glomerular lesion is characteristic of later toxemias of pregnancy and that it might be explained on the basis of a soluble toxic substance in the blood stream rather than as a result of arterial spasm as suggested by Volhard.

Acosta-Sison and others, however, have expressed the opinion that vascular damage is the principal etiologic factor in the pathologic changes in the heart, liver, kidneys and brain, and Addis has accepted the hypothesis that *angiospasm* frequently underlies the vascular pathologic conditions. He noted that the effects of spasm in various organs may lead to entirely different syndromes: in the brain, to hypertensive encephalopathy; in the kidney, to disturbance of function; in the liver, to periportal thromboses, and in the subcutaneous tissue, to anasarca. A single factor is thus responsible, through its action on various tissues, for widely divergent manifestations. According to Herrick, the mild and severe toxemias differ in degree, rather than in kind, the rôle of vascular spasm being equally important in both.

If one accepts the evidence that hypertension is the result of angiospasm of unknown origin and that vascular spasm is an accompaniment of the late toxemias of pregnancy, then *hypertension* becomes an important symptom of the disease. There is, moreover, the suggestion that manifest hypertension is preceded by generalized arteriolar spasticity, especially exhibited clinically by retinal and glomerular vessels.

That the late toxemias may lead, after termination of the

pregnancy, to *chronic cardiovascular and renal disease* has been emphasized by Corwin and Herrick. Chronic nephritis after eclampsia has been observed by Caldwell and Lyle, Gibson,¹⁰ Harris and others, and Peckham²⁴ has pointed out that the duration and severity of the toxemia are related to the incidence of later chronic nephritis. One may thus form the hypothesis that the arterial spasm, which is a factor in producing the familiar symptoms of preeclampsia and eclampsia, is initially a temporary and reversible phenomenon, but, if continued over a long enough period, may become permanent by virtue of adding structural changes to the early functional alterations.

That the retinal vessels, however, show a *difference* between the changes produced by *arteriosclerosis* and those due to the *acute toxemias* of pregnancy has been noted by accurate observation. Wagener described the development of visible alterations in the retinal vessels in the acute toxemias: "In cases of toxemia of pregnancy in which there is an associated rise in blood pressure, changes in the arterioles appear first and those in the retina proper, commonly called 'retinitis,' are secondary to and apparently dependent on the changes in the arterioles. The caliber of the arterioles appears narrowed and the lumen is reduced because of spastic contraction and increased tonus in the walls of the arterioles. This change in the arterioles may disappear entirely if there is early and permanent fall in blood pressure. The constriction soon becomes fixed if the toxemia progresses. When the constriction of any arteriole becomes so fixed and severe as to cause secondary capillary ischemia or stasis, localized edema and hemorrhage appear in the adjacent retina. If the toxemia continues, this spastic constriction may become so generalized and severe as to produce diffuse retinitis of the albuminuric type, the classic 'retinitis of pregnancy nephritis.' The presence or absence, or the advancement of the involvement of the arterioles can be determined best by frequent systematic examination of the retina." Wagener also has called attention to the fact that acute vascular changes in the retina may be superimposed on previously sclerotic vessels.

A convenient grouping of these changes into *four consecutive stages* may be made on the basis of this description

and is found to be related to the severity and duration of the hypertension accompanying the toxemia: (1) The first sign is spastic narrowing of the arterioles of the retina, which may affect all branches of the central artery. (2) Then appears irregular constriction of the lumina of the arterioles, which may vary in location from day to day and is usually more severe in the nasal branches. (3) The narrowing and constriction become more fixed, and individual cotton-wool patches and hemorrhage may appear on the retina. (4) Diffuse albuminuric retinitis appears.

In a previous paper I¹⁰ analyzed the observations made on 108 patients who had late toxemia of pregnancy and indicated the correlation between severity of the hypertension and the degree of retinal vascular damage. Those patients with systolic blood pressure of more than 200 mm. of mercury all showed retinal changes, most of them severe. Only 10 per cent of patients with pressures between 170 and 199 mm. of mercury were free of retinal changes, but only 22 per cent showed damage of grade 3 or 4 on a basis of 1 to 4. In the groups with blood pressures between 140 to 169 mm., nearly 50 per cent showed no retinal changes, and only 2 per cent (one case) had damage of more than grade 2 intensity. Fourteen of this series had pre-existing hypertension.

A parallel between retinal changes and the *severity* of the hypertension, and consequently the toxemia, was noted by Schultz and O'Brien. Of forty-seven cases of late toxemia, approximately one-half had visual disturbances. Those with normal fundi had an average blood pressure of 165 mm. of mercury systolic and 109 diastolic. In those with angi sclerosis, the average pressure was 181/118 while in those exhibiting an actual retinitis the pressure rose to 199/137.

In routine examination of pregnant women, Masters observed narrowing of the retinal arteries in all cases in which the systolic blood pressure was *more than* 150 mm. of mercury. Wagener found changes in 70 per cent of a series of fifty cases with pressures greater than 140 mm. and no previously existing hypertension. McCord reported recently that 82 per cent of 231 cases of acute toxemia had positive retinal findings.

Gibson¹¹ agreed essentially with the observations and conclusions of Wagener and characterized the steps in the progres-

sion of retinal vascular damage as *attenuation*, *angiospasm*, *angiosclerosis* and *retinitis*. The two former he called "pre-organic," that is, present before permanent changes appear. If the vascular damage does not subside with the toxemia, the organic stage sets in, with sclerosis of vessels. A latent stage of four to twelve years succeeds, when hypertension is mild and no symptoms are present. Finally a terminal stage appears in the guise of renal or cardiac insufficiency, or hypertensive encephalopathy. Gibson reported that of thirty-nine patients in whom acute late toxemia of pregnancy developed, the fundi of five showed no changes, twenty-three had pre-organic, hypertensive changes, and eleven had organic, sclerotic changes.

On the other hand Dieckmann and Brown stated: "Ophthalmoscopic examination, even though made by an experienced ophthalmologist, has been of little aid to us, either in diagnosis or prognosis." They noted some abnormal changes in the retinal vessels of 35 per cent of patients who had mild preeclampsia and more extensive pathologic changes in the retinas of 47 per cent of patients who had severe preeclampsia. All the vascular lesions disappeared within two weeks postpartum.

In Peckham's²² early series of cases, *chronic nephritis* subsequently did not develop in any whose systolic pressure remained less than 170 mm. of mercury, but 15 per cent of those with pressures between 170 and 200 mm. and 48 per cent of those with pressures in excess of 200 mm. showed evidences of nephritis postpartum. Later, after further clinical observation, Peckham and Stout reported that approximately one-half of a group of cases diagnosed as a low reserve kidney (which is considered by some to correspond to mild late toxemia or mild preeclampsia) showed five years later signs of chronic arterial or renal disease.

Because chronic renal or hypertensive disease may antedate pregnancy and be aggravated by it, in the first or early in the second trimester, it is valuable to be able to recognize the sclerosis of the retinal vessels which may be apparent even before tests of renal function indicate the presence of disease. Frequently there are generalized narrowing of the retinal arterioles, increased light reflex, tortuosity, and indentation of

veins at arteriovenous crossings which tend to be right-angled. There may be flame-shaped hemorrhages, cotton-wool exudates, or a star-shaped macular figure. The last picture represents an irreversible process and is striking evidence of generalized vascular damage throughout the body. In such cases termination of pregnancy is usually indicated, although patients with mild hypertension or occult nephritis may pass through their pregnancy with no exacerbation of their condition.

The bearing of *ophthalmoscopic retinal examination* on the management of acute hypertensive toxemia deserves brief mention. The severity of the disease is evidenced by the usual signs of hypertension, albuminuria and edema, together with symptoms of headache, visual disturbances and epigastric pain. In most cases where these findings are pronounced, ophthalmoscopic examination will reveal changes in the retinal vessels and may aid in the decision whether or not to terminate pregnancy. Treatment of preeclampsia and eclampsia involves the use of sedation, limitation of diet, salt and fluids, and careful employment of magnesium sulfate or glucose solutions. Most patients will respond favorably to such conservative medical therapy, but some will fail to improve or will suffer a relapse following initial regression of symptoms, and only radical measures can effect a cure. Rarely must the pregnancy be terminated when the systolic pressure is less than 160 mm. of mercury and the toxemia is mild. Almost always labor must be induced when the pressure is persistently 180 mm. or more in cases of severe, nonconvulsive toxemia; the question of termination or of noninterference is a difficult one when the toxemia is moderately severe and the pressure remains between 160 and 180 mm. Repeated examination of the eye grounds will usually not only show the extent of pathologic change but may indicate whether the process is stationary, advancing, or receding.

On the obstetric service at St. Mary's Hospital, in the presence of mild symptoms of toxemia, pregnancy has been allowed to continue when the retinal vessels appeared normal or showed stationary lesions. In other cases I believe that the progression of toxemia has often been avoided by interrupting the pregnancy in which advancing vascular changes were noted in the retina. In a group of cases previously reported, retinal ex-

amination was of diagnostic value in 83 per cent of 140 cases, although it was not the sole means by which a decision to continue or to interrupt pregnancy was reached.

The *persistence* of vascular lesions in the retina should be interpreted as a warning even though clinical symptoms appear to be waning. On the other hand, a fullblown, toxicemic condition must be treated *per se* regardless of the retinal picture.

Comment and summary.—The acute toxemias of late pregnancy are characterized by hypertension, edema, albuminuria and, commonly, demonstrable changes in the retinal vessels. The vascular pathologic changes appear to be dependent on a generalized spasm of arterioles throughout the body, which is transient in its early stages and irreversible if of long duration. There is sufficient correlation between the severity of the toxemia, the degree of hypertension, and the amount of retinal damage to render retinal examination of value in the diagnosis and management of the toxemias. Retinal examination early in pregnancy frequently permits the detection of pre-existing renal and hypertensive disease, and in the later months may reveal the superimposition of new acute lesions on old sclerotic processes.

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HEADACHE: A CONSIDERATION OF SOME OF THE MORE COMMON TYPES

HENRY W. WOLTMAN

It is not true, as some patients assert with confidence, that "everyone has headaches." However, headache is a complaint so common that remedies for it are dispensed through slot machines and so vaguely understood that most headaches have been attributed by different writers to disorders of the gastrointestinal tract, to allergic reactions, to disease of the nose, and most of them, indeed, almost without exception, to the eyes. The subject of headache is, therefore, deserving of at least passing notice. An additional excuse, if one were needed, for dwelling on the subject of headache is that a few fragments have been added to our knowledge of it.

More than thirty varieties of headache have been described and a perusal of the textbooks will indicate an amazing lack of conformity of opinions. More often than not, headache is a symptom that occurs without signs. It is this condition I should like to discuss. In this particular instance all the discussor has to lean upon are the answers to a few questions. These are fragile reeds at best, especially so if the physician fails to understand, not what the patient says, but what he thinks he says. Let the physician ask him, for example, what he means by headache. It need cause no surprise when he says that it means a sensation such as would be produced by ants crawling over the scalp. To the question, "Did you ever have a headache previous to three months ago?" he may reply, "Oh, yes, I've had headaches all my life, but they did not trouble me until three months ago." Having just said, for instance, that they occurred only on the right side of the head, he may admit that they sometimes do occur on the left side.

Likewise, the physician should inquire into the frequency, duration and exact location of the headache; the hour of night

or day and the day of the week the attacks may occur; whether they are becoming better or worse; whether there is an aura; what influences a delayed meal, late sleep, worry, fatigue, and use of the eyes have on the headache; whether stooping, jarring or shaking of the head influences the pain; whether cold drafts or local heat affects pain; whether there is a family history of headache, hay fever, asthma, eczema, urticaria or angioneurotic edema, and whether particular foods precipitate a headache; whether there is evidence of infection or obstruction in the nose or ears; whether the menses or pregnancy influence the headache, and finally, what previous treatment has been received. Nor must it be forgotten that a patient may have two kinds of headache; the one, perhaps, of little consequence; the other, perhaps, the symptom of a fatal illness.

Before considering some of the more important varieties of headache I should like, for the sake of emphasis, to stress the need for examining the eye grounds carefully in every case and the necessity of making good stereoscopic roentgenograms of the skull in at least lateral and anteroposterior directions.

A return to the patient will reveal what his story suggests.

The headache of increased intracranial pressure.—

Perhaps the patient's headache is relatively recent in onset, and is causing more and more discomfort; it is situated in the front or in the back of the head, or, if predominantly one-sided, recurs in the same situation. Possibly, also, the headache awakens the patient early in the morning, and may be accentuated or precipitated by coughing, stooping, straining, or shaking of the head. There may be associated with it, also, sudden vomiting, especially before breakfast, and the pulse, if felt carefully for two or three minutes, may be observed to become slow and irregular at times. I have not seen this in the presence of migrainous headache even though the pain may be as intense as that which is associated with tumor of the brain. Such a headache suggests organic intracranial disease and increased intracranial pressure, and this in turn suggests the possibility of tumor of the brain. To be sure, there may be no headache whatever in the presence of tumor, even when the intracranial pressure is elevated, and there may be headache with tumor, even when the intracranial pressure is low. Tapping of the ventricles may either relieve the pain or cause it.

The injection of histamine may reproduce the headache, which suggests that, even when tumor is present, the pain may arise from the arteries.

An intense, recurring occipital or frontal headache, of sudden onset and termination, lasting a few minutes to a few hours, which is associated at the time with nystagmus, vertigo, rigidity of the neck (often in extension, less often in flexion) which may be associated with hiccup and slowness and irregularity of the pulse, a headache in which these symptoms are present at the time of the seizure but not during the intervals, suggests intermittent hydrocephalus, and this in turn suggests a tumor in the ventricular system. Choking of the disks is often absent. During such an attack the patient may look as if he were about to die, and he often does; during the interval he may appear to be in the best of health.

The ingestion of large amounts of fluid or the giving of a standard enema may lead to disastrous results. Spinal puncture, especially in instances of supratentorial tumor, and, according to the usual advice, in instances of infratentorial tumor, is unsafe. The intravenous administration of hypertonic solutions may relieve such a headache, but may be followed later by a severe reaction. The restricted intake of sweetened fruit juices and the instillation of a hypertonic enema may be helpful.

The headaches of sinus thrombosis, meningitis and encephalitis lack well-defined characteristics, save that they are often severe and stubborn. More often than not they are attended by signs of disease that at least cause the physician to flounder among opinions regarding the many possibilities.

The development of meningitis or abscess of the brain in the course of suppurative otitis media is a danger which every physician recognizes. The invasion of the nervous system is typically a stormy one. A cloudy spinal fluid may reveal the nature of the headaches. When no organisms can be demonstrated, apprehension need not be so great as it otherwise would be, for the condition may clear up spontaneously or may do so with the help of repeated spinal punctures. Should apparent improvement be followed by symptoms and signs of increasing intracranial pressure or of invasion of the brain, an abscess may be forming. Incidentally, I should like to stress the importance of waiting until an abscess has formed before attempting to

drain one. Liquefaction and encapsulation take time, and courageous observation is bred from experience. To operate when the patient still has fever, when choking of the disks is increasing, or when neutrophils dominate the cells in the spinal fluid, is to court disaster. The introduction of sulfanilamide and other chemicals has, of course, introduced a hopefulness into the treatment of these illnesses that was altogether unwarranted before their arrival.

Headaches associated with decreased intracranial pressure.—Occasionally an occipital or frontal headache comes on only when the patient is up and about and leaves when the patient lies down. Such a headache is often associated with low pressure of the spinal fluid. Thus, it resembles postpuncture headache. Often it suggests an arteriosclerotic basis, but it may occur in younger persons, who, presumably, are free from arteriosclerosis.

Ruptured aneurysm.—In a young, healthy person who, it may be learned, has just been shoveling snow or pushing an automobile, the sudden onset of an excruciating occipital headache or of pain behind one eye suggests a ruptured aneurysm. There is often rigidity of the neck, a slow, irregular pulse, and clouding of consciousness. Also there may be backache, legache and a positive Kernig's sign. Paralysis of the third cranial nerve on one side and hemiplegia on the other are commonly present, since such aneurysms usually occur in the circle of Willis. A spinal puncture discloses free blood.

A similar story but one which includes lateralized headache and, often, less evidence of meningeal irritation, in a person who has hypertension, suggests cerebral hemorrhage.

Hypertensive headaches.—An occipital or frontal headache that may be present on the patient's awakening but which does not awaken the patient, a headache that may wear away as the day progresses, that tends to occur daily, then leaves and then recurs, suggests a hypertensive headache. The behavior of hypertensive headaches is often confusing. An especially disabling headache seems to result from the combination of migraine with hypertensive headaches. Indeed, as Hines has pointed out, the two conditions have much in common. In the presence of diffuse arteriolar disease with hypertension, group 4, the pressure of the spinal fluid is commonly elevated and

there is usually papilledema, but there is not necessarily headache, and spinal drainage may or may not relieve the headache.

In a noteworthy study of seventeen such cases with necropsy, Rosenberg found destructive cerebral lesions in 71 per cent. These included scattered large and small hemorrhages, infarcts of various sizes and numbers, periarteriolar lymphocytic cuffing, suggestive of an inflammatory reaction, gliosis, and local or general edema of the brain. Conceivably, any of these lesions may be related to hypertensive headache. The results of treatment may be discouraging. Reduction in physical and emotional tension through constructive advice, rest, sedation, spinal punctures, and venesection, may be helpful.

The passive congestion produced by intrathoracic tumors and the distention of the vessels in polycythemia, may cause distressing and persistent headache.

Arteriosclerotic headaches.—Dull, heavy bregmatic or frontal headaches or occasionally stabbing, sharply localized headaches occur in 44 per cent of patients for whom a clinical diagnosis of cerebrospinal arteriosclerosis is warranted. In this group, 64 per cent of patients have an average blood pressure of 130 mm. of mercury, systolic and 78 mm. diastolic.

In a review of 100 cases in which a pathologic diagnosis of cerebral arteriosclerosis was made, it was found that three times as many of the patients had had hypertension as had had a normal blood pressure. About one-third of patients of each of these groups (that is, those who had hypertension and those who were normal), eliminating those in whom intense headache symptomatic of terminal massive hemorrhage into the brain had occurred, had complained of headache. Obviously, headache referable to arteriosclerosis is a field deserving of further study.

Headaches referable to anomalies or inflammation of the arteries.—A sharply localizing headache of a duration of months or years induced or accentuated by coughing, stooping or straining, may result from some vascular anomaly, such as the passage of an artery through a canal in the bone.

A priest, aged fifty-five years, had experienced intense pain in the right parietal region, which appeared only when he coughed, strained, or stooped. Not a single helpful finding

could be discovered at examination. I explained the situation. He said, "Doctor, I have had this thing for five years and I simply cannot go on this way. You must open my head and see what is wrong." When a bone flap was turned down, a spurt of blood occurred that issued from a torn artery that had been embedded in a channel 1 cm. long, in the inner table of the skull. The vessel was ligated and he has been free from pain since.

Headaches resulting from diseases of extracranial structures.—Often, it is forgotten that extracranial structures, such as muscles, fasciae, nerves, and vessels, may be the seat of disease. Nothing is easier than to palpate the head, yet this procedure is often neglected. Small fibromas occurring in the course of a nerve, localized arteritis, or fibrositis may be the cause of long-continued headache. Local tenderness and induration may aid in establishing the diagnosis. Inflammation of the extracranial arteries may be painful. Excision of the firm and tender vessel may provide immediate relief. Most carefully studied, perhaps, have been those cases in which temporal arteritis was present. Inflammation and trauma of the superficial nerves likewise may be the cause of distressing headache. The flashing pains of occipital neuralgia ought to be distinguished from the more persistent pains of neuritis, although local anesthetization as a test and section of the offending nerve may be helpful in either case.

Posttraumatic headache.—Following injuries to the head—often trivial injuries—persistent local or general headaches may occur, that are usually initiated by work of any kind. The features of the patient may be drawn and careworn or grim and determined. Often the patient has a sullen demeanor and complains of giddiness, tremor, weakness and loss of memory. Some authorities are of the opinion that these symptoms are always based on some organic but not necessarily demonstrable lesion of the brain. This is suggested by the remarkable similarity of the complaints enumerated by different patients. Other authorities insist that every posttraumatic headache is psychogenic. Too often, it is to be regretted the issue is befogged by concern over compensation payments and the records are littered with the documents of solicitors. All of this would be much less disconcerting to the physician if his knowl-

edge of these complaints were greater. A settlement of the claim does not always cure the patient. Fortunately, encephalograms may reveal cortical damage, which, when it is the only objective evidence available, is helpful, but cortical damage does not always parallel the complaints. The therapeutic benefits indicated by encephalography itself are not so commonly achieved as it was at one time hoped.

It is well to note that a fracture of the skull is usually not found with that more serious complication, chronic subdural hematoma. The accelerating tempo with which mental and motor signs appear when such a hematoma is present calls for prompt action if a fatality is to be averted.

Toxic headaches.—The throbbing, frontal headache associated with fever is a good example of so-called toxic headaches. The relationship of such headaches to some more obvious cause is usually the reason for classifying them as such.

Headaches associated with disorders of the special sense organs.—Crisp wrote, "As very characteristic of eyestrain, we include especially frontal and parietal headaches, or an ache in or around the eyeball itself. But occipital and nuchal pain are frequently symptoms of eyestrain, and, at times, eyestrain leads the patient to complain of pain as low down as between the shoulder blades, which, of course, can hardly be thought of as a headache and yet is closely related to it."

When headaches are related to the ear, the history or signs of infection involving this organ usually cause physicians to consider this possibility. The retro-orbital pain of petrositis and the pain attending epidural abscess may be of long duration. Such situations challenge our courage, since the treatment involves no halfway measures.

The headaches caused by disorders of the nose, sinuses and nasopharynx incidental to infection, ventilation, contacts and tumors may be intense, but when appropriate treatment is given they often disappear at once.

Rheumatic headaches.—A more or less constant, rather superficial pain, often lasting many months, situated over the occipital, nuchal, and upper trapezius regions, which may be tender, a pain that is brought on by exposure to a cold draft or by tension of the muscles in these regions, and a pain that

is relieved by the local application of heat, suggests a nodular, rheumatic, or fibrositic headache. The eradication of foci of infection, application of local hot packs and heavy massage, are helpful.

Headaches related to endocrine dysfunction.—Probably often migrainous in their characteristics, headaches related to endocrine activities require further definition. This subject will be considered further under the heading of "migraine."

Continuous, generalized headache may occur in the presence of pituitary tumors, even when these tumors have not broken into the cranial cavity. Therapeutic radiation of the pituitary region may bring quick relief. Ryneerson has treated, with at least temporary success, a patient who had such a headache of several years' standing, by the weekly administration of 25 mg. of male sex hormone. Similar pains occurring in the head in the presence of acromegaly may depend on the same factors that sometimes cause constant pain in the acral parts of the extremities.

Migraine.—Most common of all headaches, with an incidence twice as high among women as among men, usually afflicting the ambitious members of society, with hereditary appearance almost the rule, accompanied by a history of recurrence over many years, in which the earliest headaches may have been as severe as any of the later ones, headaches that often appear under stress and at the menstrual period, but that may disappear temporarily during pregnancy, and permanently, but not always at the climacteric—these are the headaches that suggest migraine. The migrainous attack itself is often introduced by warnings such as scotoma. The headache itself usually occurs on one side of the head, but not always on the same side or in the same situation. Vomiting is not a necessary accompaniment. In 90 per cent of such cases, the headache is relieved by the administration to the patient of ergotamine tartrate, which observation, incidentally serves to identify the headache as migraine.

Much has been learned in recent years concerning the cause of these headaches. The common explanation that the pain results from edema of any part of the brain has not been proved. It is known that the larger vessels of the dura and probably adjacent parts of the dura are sensitive, that the larger arteries

at the base of the brain are sensitive, and that the tentorium may be sensitive. The brain itself and the vessels of the brain and pia are not sensitive. It seems remarkable that in the Seventeenth Century Thomas Willis (1621-1675) could write regarding the headaches of Lady Anne Conway,⁶ "Certainly it seems most likely, that the invincible and permanent cause so long and yet not deadly Headache proceeds from such a thing, viz., A Scirrhus Distemper of Dura mater, the Pia mater being in the mean time safe." Obviously, there has been little opportunity to investigate the auras of migraine. It seems likely that constriction of the pial arteries accounts for the scotomas and paresthesias. Loss of appreciation of passive movements has been demonstrated during a paresthetic aura. This indicates that more than the dural vessels take part in the attack and suggests that the cortical vessels may go into a state of spasm. Subsequently, those vessels dilate.

Although migraine involves a widespread neurovegetative reaction, of which little is known, the pain itself has been studied carefully. With the help of recording devices Graham and Wolff observed that the height of the headache coincides with an excessive pulsation of the temporal artery. They also observed that the injection of ergotamine tartrate, which stimulates smooth muscle, results, not only in reduction of the headache, but also in the reduction of the amplitude of pulsations of the temporal artery. Direct inspection of the middle meningeal artery revealed that the injection of ergotamine tartrate caused a constriction of 20 per cent in the caliber of this vessel. The caliber of the sylvian artery or vein, however, was not altered. Graham and Wolff observed further that manual compression of the temporal, carotid and occipital arteries caused the pain to subside in the regions supplied by these vessels. Ligation of the temporal artery brought about a reduction of pain at the corresponding site. The residual pain probably arose from within the skull. Following the injection of histamine, the pulsations increased again and the pain returned to its former situation. Histamine itself does not cause the pain, since there was no return of pain until after the injection of histamine had been discontinued; this means that the systemic blood pressure must return before the impact of the column of blood upon the cerebral vessels is sufficient to cause pain.

Thus, it would seem that the pain of migraine results from the stretching of relaxed dural arteries by the shock of arterial pulsation.

The pulsation of the cerebrospinal fluid or its pressure could not be correlated directly with the intensity of the pain, nor were these two factors constantly influenced by the injection of ergotamine tartrate. Other observers, however, have reported that an increase in the pressure of the spinal fluid occurs after the injection of ergotamine tartrate. Any increase in pressure of the spinal fluid would, to be sure, tend to support the vessels.

The injection of ergotamine tartrate also increases the blood flow and the oxygen-carrying capacity of the arteries and veins. Possibly this may be correlated with the recent observations of Alvarez that the inhalation of oxygen may relieve migraine, especially if it is inhaled early.

These observations seem to explain the relief from pain that occurs in 90 per cent of cases following the administration of *ergotamine tartrate*. The early oral administration of 1 mg. twice daily during an attack of pain, or of 0.5 mg. given subcutaneously, produces strikingly good results. Placed under the tongue, ergotamine tartrate is much more effective than when it is swallowed directly. Some observers administer as much as 5 mg. orally in a single dose, and from 1 to 2 mg. each hour thereafter until a total dose of 10 to 12 mg. in twelve hours has been administered. The initial subcutaneous dose is generally 0.25 mg.; not more than 0.5 mg. should be given subcutaneously in twelve hours. Contraindications to the use of ergotamine tartrate are coronary disease, peripheral obliterative disease, acute infections, and hepatic and deficiency diseases. Gastro-intestinal symptoms, a sensation of pressure in the breast, and pain and paresthesias in the limbs may be relieved by the administration of calcium or atropine.

As an interval treatment, ergotamine tartrate is not recommended. Calcium gluconate and viosterol may be prescribed as prophylactic measures, especially for patients who complain of gastro-intestinal symptoms or allergic phenomena. Chondroitinsulfuric acid may also be helpful in this situation.

Migraine often disappears during pregnancy, when the follicular hormone is circulating. Some patients respond very well to the administration of estrogenic substances.

In the *treatment* of migraine, attention should be given to physical and emotional stresses, refractive errors, gastro-intestinal disorders, allergic disturbances, and faulty habits of all kinds. Vacations are often helpful. The administration of $\frac{1}{2}$ grain (0.032 gm.) of phenobarbital three times daily over an extended period may be useful.

"Erythromelalgia of the head."—A unilateral headache, without hereditary incidence or an early history of migraine, a headache of sudden onset and termination, in which the pain tends to awaken the patient at night, which is eased by the erect or sitting posture, which is associated with lacrimation and stuffiness of the nostril, and which is often precipitated by taking alcohol, is suggestive of "erythromelalgia of the head." There are no scotomatous or gastro-intestinal accompaniments. The injection of 0.3 mg. of histamine will produce such an attack. Desensitization to histamine by the injection twice daily of 0.05 mg. for two days and subsequently increasing the dose to 0.1 mg. for two or three weeks may result in relieving the patient entirely.

Headaches are said to occur occasionally in the presence of gastritis. The insertion of a jejunal catheter for feeding may relieve the headaches. The headaches may recur promptly, however, should the catheter slip, inadvertently, into the stomach, as may be determined by roentgenoscopy. Gastric dilatation and atony of the stomach during an attack of migraine have been observed roentgenologically.

Psychoneurotic, psychotic, neurasthenic and exhaustive headaches.—A headache that has been present constantly for months on end, one that is often poorly and resentfully described by the patient, is suggestive, not of an organic disease, but of a psychiatric disturbance. The sensation of pulling or drawing in the occipital region, or of a weight on the head, is commonly mentioned by patients who are depressed. In the presence of hysteria there may be a striking indifference of the patient to the headache when subjects other than the pain are discussed. This indifference is sometimes, no doubt, a means of escaping responsibility. In the presence of schizophrenia, also, the complaint of more or less constant discomfort in the head is not unusual.

CONCLUSIONS

When headache is the patient's chief complaint, the causes to be considered are almost without number. A thoughtfully taken history should lead the physician into paths leading to further investigation. A detailed examination may not be neglected. Nor should a careful inquiry into the emotional state, which so often plays a significant rôle in the production of headache, be disregarded.

Among the more recent advances in the understanding of this common complaint I should mention three: First, there are the observations made by Wolff and his colleagues; namely, that in migraine an increased arterial thrust upon the toneless but sensitive dural and extracranial arteries is the cause of the pain, and that the administration of ergotamine tartrate, by restoring tone to these vessels, lessens the violence of the pulsations and thus reduces the pain.

Second, I should mention the searching studies made by Rosenberg of so-called malignant hypertension, in which he demonstrated the extent of cerebral damage that is associated with this disease.

Third and finally, reference should be made to the segregation by Horton, MacLean and Craig, of a type of headache that has certain clinical characteristics and that is amenable to desensitization with histamine, and to which they have given the name "erythromelalgia of the head."

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MIGRAINE

WALTER C. ALVAREZ

One of the common diseases which the gastro-enterologist sees every week is migraine. The patients go to the gastro-enterologist because they feel so sure that the cause of the trouble is in the digestive tract and particularly in the liver. They get this idea because in attacks they vomit green bile. Actually, this doesn't mean that there is anything wrong with the liver; it means only that vomiting is commonly preceded by, or associated with reverse peristalsis in the small bowel. This causes bile to flow from the duodenum into the stomach. Such reverse peristalsis is almost certainly due to a sort of storm that comes down the vagus nerves to stimulate the small bowel. It is probably the same sort of storm that comes down the vagus nerves to produce the vomiting of seasickness and Ménière's disease.

Recently Morlock and I have found that migraine is less frequent in patients with definite disease of the liver and biliary tract than it is in persons who show no sign of such disease. Curiously, when signs of hepatic cirrhosis appear in a person who has had migraine, the headaches commonly disappear or become much milder.

WHAT IS MIGRAINE?

Recent studies have shown that migraine is a hereditary disease of the brain or of the sympathetic nerves which supply the blood vessels of certain parts of the brain. In most cases what seems to happen is that certain meningeal blood vessels dilate, and the blood goes pounding through them to produce the headache. As one might expect from this, some persons with migraine can stop a headache instantly by pressing with the finger on the carotid or the temporal artery. Unfortunately the pain returns as soon as the pressure is removed. Ergotamine tartrate or gynergen relieves many patients with mi-

graine, apparently because it causes contraction of the arteries and stops the surging of blood through them.

There is another type of unilateral headache associated with dilatation of the carotid and its branches which has recently been described by Horton, MacLean and Craig. The patients are usually more than forty years of age. The pain is excruciating. It comes and goes suddenly, often at night. The face is often flushed on one side, the eye waters on that side, and the nose on that side is blocked. There is no gastrointestinal upset with these headaches. An injection of histamine will bring on a headache, and desensitization to histamine by daily injections will usually bring relief. Desensitization to histamine helps in occasional cases of what appears to be migraine.

TREATMENT DIRECTED TO THE AVOIDANCE OF ATTACKS

Although the frequency with which attacks of migraine occur is dependent mainly on the degree of irritability of the brain, and although the disease is often thought of as a distant cousin of epilepsy, in my experience drugs like phenobarbital, bromides and sodium diphenyl hydantoinate (dilantin) which work so well in blocking attacks of epilepsy, seldom have any beneficial influence on the frequency of migrainous attacks. This would indicate again that the little storm, whatever it is, arises in the cervical sympathetic ganglions.

One would expect any disease which nags at the nervous system and makes it more irritable to increase the frequency of migrainous attacks, and one would expect the removal of any such disease in perhaps gallbladder, appendix or uterus to bring great relief. Actually, in my experience, the removal of diseased abdominal organs has rarely had any influence on the frequency and severity of the attacks. Because of this, when today I see a patient with severe migraine, I have little desire to examine him or her from head to foot because even if I were to find organic disease somewhere, I would have no hope of curing the migraine by having some operation performed.

Actually, today, it is most unfortunate that when the sufferer with migraine, often an overworked mother or secretary with little money to waste, goes first to one clinician and then to another seeking relief, about all she gets is just another pro-

longed and expensive examination, made with the hope of finding the cause of the disease. Rarely do I meet a physician who realizes that it is useless to search below the neck for the cause of the disease, and rarely do I meet one who knows how much more helpful he could be to his migrainous patients if he would only spend the time that other men spend on a complete overhauling, in asking questions, in getting acquainted, and in learning of the trying problems that come up daily in home and office. Usually, if a physician were to do this he would be astonished to find what a peculiarly sensitive and overly reactive person the migrainous patient is. Most persons with severe migraine have a peculiar and characteristic personality. They are overly reactive to emotion and overly sensitive to all stimuli. They are often highly conscientious, restless persons who are always overworking or worrying or taking life too seriously. They commonly suffer from insomnia, and they do not make sufficient effort to save the brain from fatigue. Usually they are well above average in intelligence, ability, and drive, but often they need stability and self-discipline. Some are a little psychopathic and are wearied by their efforts to adjust to life. Often a patient who is having three severe attacks a week can be almost cured by a long rest: by getting away from work, responsibilities, conflict, strain and unhappiness.

Obviously, then, the physician who really wishes to help a patient with migraine must spend most of his time, not on laboratory and roentgenologic examinations, but in finding out what are the individual's trials and tribulations, and how some of them can be overcome or avoided.

Because these patients are so sensitive to every stimulus, they naturally are often sensitive to certain foods, and commonly they know that if they eat chocolate or onions or drink milk or alcoholic liquors they will get a headache. Then further study may show that they are sensitive to wheat or to some other food. My experience leads me to believe that it is only the occasional patient who can be cured by the removal of certain foods from the diet. I recently saw a patient whose attacks stopped when I told her to stop using a karaya gum preparation for the relief of constipation.

To show what can be done by rest alone, I need only cite

one case, that of a young woman who, when I saw her eighteen months ago, was having three severe headaches a week. She was worn out then with overwork, worry, suffering, insomnia and poor mental hygiene. All she had gotten from much doctoring was a series of complete overhauls. When she was induced to leave her trying job and go home to rest under the ancestral roof, she improved rapidly until now she goes six or seven weeks without a headache.

It is possible that before long a really effective drug can be found in some one of the hormones which is formed in large amounts during pregnancy. As everyone knows, most women lose their migraine during pregnancy or after the menopause. When we physicians understand this relation of the disease to the ovarian functions we can probably cure it.

THE TREATMENT OF THE ATTACK

Now for the treatment of the attack. Usually two big mistakes are made by the patient. One is to put off taking medicine as long as possible, in the hope that it will not be necessary, and the other is to depend on drugs taken by mouth after nausea has set in. Actually, treatment for an attack should be instituted *the minute the patient thinks the headache is coming*. All treatments work poorly after the patient is exhausted with suffering. Furthermore, *after* nausea has set in, it is generally useless to put medicine into the stomach because it will not be absorbed. To be effective medicine must then be injected hypodermically or given in a rectal suppository.

A wise old physician need only look over the long list of drugs that have been used in the treatment of migraine to realize that none of them is likely to be of much value except perhaps in the milder attacks. Once a *severe* attack gets under way there are only two remedies that are likely to stop it: one is a hypodermic injection of from 0.25 to 0.5 mg. of gynergen, and the other is the inhalation of 100 per cent oxygen for one or two hours.

Gynergen, which comes in ampules containing either 0.5 or 1 c.c. of solution, is efficacious in perhaps 80 per cent of the cases, and oxygen is efficacious in perhaps the same group. Exact figures are not yet available. Some patients get relief by taking from one to four 1 mg. tablets of gynergen by mouth at the beginning of an attack. However, this use of the drug

seems unwise when the attacks are coming frequently. Under such circumstances the dose will be rather large, and in time injury may be done to the arteries. If only because attacks of migraine often come at night when it is not easy to get a physician quickly, the patient or a relative should be given a hypodermic syringe and taught how to give the injections.

From a large experience with gynergen given hypodermically once or twice a week, I can say that only rarely does the treatment have to be stopped because of alarming sensations in legs or arms. However, I wouldn't like to let a patient take the drug every day for any length of time. As Comfort has shown recently, in some patients, perhaps with an idiosyncrasy, daily doses can suddenly produce serious injury to the blood vessels.

Unfortunately, some of the persons who can relieve their headaches with gynergen must hate to use the drug because of its unpleasant after-effects. Some persons feel uncomfortable for several hours afterward. Particularly in these cases oxygen should be tried because when its inhalation brings relief this is so complete that the patient can immediately go back to work.

The patient who wishes to try the *oxygen treatment* can first breathe the gas from a physician's basal metabolism machine, or he can go to a hospital and have the anesthetist give it. Pure 100 per cent oxygen should be breathed for at least an hour or two. In those few bad cases in which later, after a few hours, the headache starts coming back, another dose of oxygen can be taken. Several persons have written me that their physician was afraid of oxygen and would not allow its being breathed for more than a half hour at a time but I feel sure this warning would not have been given if the matter had been discussed with some expert on the subject. Fine, of Boston, has shown that pure oxygen can be breathed safely for eight hours and longer, and Dr. Boothby has no fear of using it for long periods of time.

If the patient does well with the oxygen treatment he or she can then go to the expense of buying a B. L. B. mask and a reducing valve and perhaps a flow meter.* The valve should

* The mask and apparatus can be obtained from firms that in every city of any size supply hospitals and physicians.

be set to allow a flow of from 6 to 8 liters a minute. This should be just enough to keep the rebreathing bag from going flat during each inspiration. The first expense is about fifty dollars, but once the patient has the equipment in the home the expense of a treatment is small.

When first testing either gynergen or oxygen the patient must not be discouraged if an occasional treatment fails to work well. Not infrequently a headache will come when the patient is so tired or so upset psychologically that no treatment can be expected to bring prompt and complete rest to the nervous system. Much may depend also on the promptness with which treatment is instituted.

Another difficulty in treating many highly migrainous persons is that they have two or more types of headache or digestive upset, and the nonmigrainous attacks will not respond to the specific treatment. Commonly they wait too long, hoping that a mild headache will pass off and prove not to be the forerunner of a severe migrainous episode. By the time they can tell that a migrainous attack is upon them, no treatment will work well.

Sometimes it is well to *combine* treatments. Especially when gynergen or oxygen tends to relieve the headache but not so much the nausea, or when the headache, after being relieved, tends to come back in a few hours, it is often helpful to give a rectal suppository of 2 or 3 grains (0.13 or 0.2 gm.) of nembutal. This quiets the vomiting center, and it may bring on a salutary sleep.

Some patients with a mild migraine can get relief if they will take a big dose of aspirin, phenacetin, acetanilid, sodium salicylate, caffeine, or bromural the minute the headache appears. If a patient's job permits, it helps greatly also to give up work quickly and to lie down in a darkened room. If sleep comes the attack is likely to be aborted.

Between attacks, the patient should make great efforts to keep the brain quiet by getting rest, and avoiding overwork, worry, excitement, annoyance, loss of temper and loss of sleep. If the patient will insist on fighting with a spouse or relatives or overworking or worrying over trifles, the attacks will continue to come at frequent intervals and then the good effects of any form of treatment are likely some day to be exhausted.

Already I have heard from two women who instead of making the necessary efforts at self-discipline relied on taking oxygen daily; now after a year they are finding that the treatment sometimes fails to work.

It is an axiom with me that any person who is getting more than two attacks of migraine a week is using his or her brain badly and unwisely. Usually in such cases one finds that there is an unhappy situation at home for which the patient's psychopathic behavior is partly responsible. These patients cannot expect to be helped unless they will make great efforts at *self-discipline* and *self-rehabilitation*.

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PROGNOSIS IN POSTENCEPHALITIC BEHAVIOR DISORDERS

PHILIP H. HEERSEMA

During the past twenty-five years the medical world has become increasingly aware of the diagnostic possibilities in encephalitis. Since 1917, when Von Economo formulated his classical description of epidemic encephalitis, a much more tangible concept of the whole subject of encephalitis has obtained. It has been assumed without convincing proof that encephalitis lethargica is caused by a filtrable virus. Some form of virus has also been considered to be the etiologic agent in other encephalitides, particularly that type of encephalitis characterizing the St. Louis epidemic, Japanese encephalitis (also called "summer encephalitis"), and equine encephalitis. Because these various forms have some features in common and because each may definitely be classified as an encephalitis with the potentiality of sequelae, the net result has been to put all virus diseases under suspicion when considering the late sequelae of any inflammatory attack on the brain.

It is now recognized that the severity of the acute attack has little relationship to the severity of the sequelae. This is well borne out by the frequent difficulties encountered in attempting to find any history of a significant illness to account for an undeniable postencephalitic syndrome which a patient may present. Until specific viruses are shown to have a definite and exclusive effect in producing the sequelae of which I speak, it would seem legitimate to entertain suspicion toward the whole virus group of diseases. Therefore, it would not seem to be presuming too much to attribute these sequelae to an *antecedent* illness such as mumps, measles, or other similar diseases. It must be considered significant when there are symptoms such as hypersomnolence or reversal of sleep routine, diplopia, or an ocular palsy and a mild state of confusion

associated with what might otherwise appear to be typically a mildly contagious disease of childhood. If the neurologic findings persist or if a change in personality and behavior follows directly upon this acute illness, the relationship must be accepted or at least seriously considered.

Diagnosis.—Postencephalitic behavior disorders appeared as one form of the sequelae which became prevalent in sufficient numbers to attract the attention of the entire profession within one or two years after the epidemics of "sleeping sickness" and the "influenza" of 1918 to 1920. In those instances which one might term as being pure "behavior disorders," that is, conditions in which there were no associated organic neurologic stigmata, it is not always easy to make a diagnosis. Any physician who includes pediatrics as a part of his practice is familiar with the difficult problems in behavior that may be demonstrated with purely psychogenic backgrounds. Actually, the postencephalitic behavior disorder is sometimes diagnosed only after the child fails to show the slightest response to the usual psychotherapeutic methods utilized in the management of reactive behavior disorders of a psychogenic type.

Typically, postencephalitic behavior disorders are characterized by impulsive, aggressive behavior ranging from repeated acts of mischief to asocial acts of a criminal character. Emotionally, the child is extremely volatile. Signs of affection are usually exaggerated and mawkish when they are present. Such children are subject to demonstrations of irritability and acts of unwarranted cruelty about which there is rather obvious evidence of a driving, compulsive force which Kahn aptly terms "organic drivenness." This force may take some rather bizarre forms of expression in the physiologic as well as the sociopsychologic fields. For example, in 1927, Snell and Rowntree reported a case in which the patient's condition was diagnosed as diabetes insipidus secondary to epidemic encephalitis. This patient demonstrated remarkable intake of water, the quantity ranging from 20 to 60 liters a day, although the patient insisted that his was "not a real thirst." The authors have described this as a compulsive thirst which appears to be similar in character and force to the driving behavior caused by postencephalitic behavior disorder. Some idea of the force of this compulsion in this patient is evidenced

by the fact that occasionally the hydration and water intoxication was sufficient to produce convulsions.

The present discussion of the sequelae of encephalitis is principally concerned with the personality and behavior changes in children which may be grouped under the heading of "postencephalitic behavior disorders." In a clinical sense, behavior disorders are rather infrequent if the physician deals only with those patients who are free from any obvious neurologic stigmata subsequent to the acute illness, since minor neurologic signs such as unequal reflexes, ocular paresis and tics frequently occur in conjunction with changes in behavior. In my experience, these minor residual evidences of encephalitis do not in themselves change the prognosis of an associated behavior problem and therefore, if the neurologic defect is minimal and static, they should be considered primarily from the standpoint of a behavior disorder. The *symptoms of initial encephalitis* include headache, mild fever and general malaise, somnolence or disturbance in sleep rhythm, visual disturbances such as weakness, blurred vision or diplopia and fasciculation of the muscles of the face, choreiform movements and even paralytic symptoms of the extremities. These features may practically disappear on recovery of the patient from the acute stage and it may be very difficult to obtain a significant history of these symptoms as being related to any acute illness when attempting to establish evidence to explain the appearance of encephalitic sequelae, months or years later. This difficulty has become more and more prevalent during the past few years, during which patients suffering from encephalitic sequelae have been coming to The Mayo Clinic in the absence of any epidemic which would sufficiently arouse the local physician so that he would consider encephalitis as the differential diagnosis during the patient's acute illness.

This is exemplified by the following report:

REPORT OF A CASE

Case I.—A girl, ten years old, had suffered a rash which was undoubtedly correctly diagnosed as measles in May, 1939. She had exhibited more than the usual amount of the febrile somnolence and irritability at this time, but it had been attributed to intestinal upset and general malaise rather than to any encephalitic manifestations. No examination of the spinal fluid had been made because the presence of encephalitis was not suspected. Convalescence had

been marked by petulance and irregular habits readily excused by the parents. Six weeks after this illness, the patient had suffered a moderate cranial injury when she was thrown from a bicycle and it was reported that she had been unconscious for about five minutes. The child had been away from her parents for about three weeks at this time and when they again saw the patient, a distinct change in personality had been noted as evidenced by restlessness, impulsive acts, demonstrations of cruelty, compulsive tic-like movements of the face and an inability to get along with playmates, all of which had been completely foreign to this child's personality six months before.

Neurologically, this child was normal with the possible exception of the grimacing which became worse under stress of reprimands.

This case exemplifies the difficulty of diagnosis in which the physician must consider the causation of the condition as a mild disease of childhood, with an apparent insidious progression of the personality change, as opposed to the traumatic episode. Probably the trauma suffered by the aforementioned child served to accentuate mild changes of personality which resulted from the infection. The similarity of the sequelae of inflammatory and traumatic conditions warrants their clinical classification as "behavior disorders of the postencephalitic type." This similarity has been pointed out and supported by a number of well-chosen cases by Strecker and Ebaugh. It should further impress physicians with the need of being constantly aware of the character of postencephalitic behavior disorders in spite of the absence of epidemics of encephalitis, influenza or the more recent forms of encephalitis. In other words, the *acute infectious diseases of childhood*, especially those of a virus type, and the numerous traumas of childhood, must be considered as potential etiologic agents. Bond and Appel in their excellent report of behavior disorders treated at the Franklin School stated that the more acute the symptoms of the initial illness, the more severe will be the conduct deviations which follow. In general, this may be true but during the past five years, we of The Mayo Clinic have been considerably impressed by the absence of good histories of the initial illness in certain cases in which the evidences of encephalitic sequelae were very definite.

It is important to note that the postencephalitic behavior disorders occur *almost exclusively* in children and adolescent persons. Essentially, these disorders lie in the emotional sphere. With this in mind, it is of significance to note the

character of the encephalitic sequelae in the child or adolescent person as compared with the adult person. Paskind has reported seven cases of encephalitic sequelae in which "mental disturbance" was the chief sequel. In three of these cases, the onset of the initial illness occurred before the patients reached the age of sixteen. In each of these three cases the type of mental disturbance present was that of antisocial behavior, although the behavior history had been essentially normal before the onset of the illness. On the other hand, in only one of the four adult patients was there any antisocial behavior, this one instance being an acute episode of homicidal irritability provoked by an argument. That is to say, although abnormal emotional reactions may occur in the adult patient who has encephalitis, these reactions are often an exaggeration of former unfavorable personality features, whereas in children, complete change of behavior is more often the case. Encephalitis in itself carries little danger of intellectual deterioration in the adult patient, although the patient's psychologic reaction to his incapacity may be very profound.

Pathology.—It is rather well accepted that encephalitis contracted *before* the patient reaches the age of *five years* carries with it great danger of mental deficiency as a residual effect. It is equally well recognized, barring any unusual environmental features, that a child's intelligence quotient and ability to learn is fairly well established at the age of five or six years, and remains rather constant thereafter. Therefore, the age of vulnerability would seem to be determined by the stage of brain organization present. In children, in those cases in which the patients survive the initial attack of encephalitis, and in which there are resultant disorders of behavior, the attack may not have been severe enough to cause any considerable motor damage, yet it may seriously affect the behavior of the child because the disease has in general interfered with organization of the brain or the organizing processes of the development of the brain. The assimilation of sensation, perception of new concepts and of moral values and acknowledgment of social restrictions are all gradually being organized into a working unit by the individual before the end of the adolescent period. In the typical postencephalitic behavior disorders, it is known that these are the behavior elements which are the most

severely affected. A few careful pathologic studies of the brain in a postencephalitic behavior disorder might enlighten physicians considerably in regard to the situation and character of the damage.

It is my opinion that the damage preceding the behavior disorder occurs largely in the frontal lobe and is diffuse and relatively mild, so that six months after recovery of the patient from the acute phase of the illness it is possible that no pathologic process could be detected. Since these patients do not die of the behavior disorders, in themselves, the opportunities for careful histopathologic study obviously are very rare. The congestion and edema and small punctate hemorrhages which are found during the acute stages probably disappear entirely. In the case of the child who has recovered to the extent that his condition represents only a behavior disorder, without any objective neurologic damage, it may be assumed that the disease has temporarily or permanently disorganized (retarded) the developmental processes rather than produced objective histopathologic evidence of destruction.

The argument for the existence of a *chronic* encephalitic process becomes forceful, it is true, when the condition of a girl who suffered encephalitis at the age of ten and in whom a behavior disorder had been an immediate sequel, is considered. She showed remarkable progress for about ten years and was considered to be essentially normal, only to be attacked by parkinsonism about fourteen years after the initial illness. Nor is this an isolated instance of such a progression. However, it is rare enough so that the possibility of a re-infection or even a mild subsequent infection superimposed upon vulnerable tissues, might be considered in the history of this patient.

Prognosis.—It is not my intention to introduce speculation as a substitute for fact. In simple terms, the *prognosis* in encephalitic sequelae is poor. It is definitely worse than the most pessimistic predictions of twenty years ago, but I am sure that physicians are not willing to throw up their hands in despair and make no attempt to stem the relentless progression of the sequelae of the encephalitides. If the postencephalitic behavior disorders may be considered functional, until proved organic by definite involvement of anatomic neurologic structures, then it may be assumed that the battle is not hopeless. The problem may concern changes in technic of handling pa-

tients who have acute attacks of the disease, improvement of methods of managing the convalescence of the patient, of intensive training and re-education of the patient at the first sign of disturbed behavior sequelae. It may be that all periods are of equal importance; the acute illness and convalescence from the prophylactic standpoint and the sequelae from the standpoint of adjusting the individual to damage which has occurred. To date, management has availed but little in terms of improvement. One of the most valuable projects of rehabilitation of children who have been afflicted with personality and behavior changes has been undertaken by Bond and his associates in establishing the Franklin School of the Pennsylvania Hospital. This school, begun in December, 1924, has served as a pioneer in enthusiastic but scientifically honest and psychiatrically judicious approaches to the control of these behavior disorders resulting from encephalitis.

Statistically, as a whole, the results of Bond and his associates have been disappointing, although entirely justified in consideration of actual improvement of individual conditions, let alone in the value to the community in relieving it of the pernicious influence of these unfortunate children upon their playmates. Smith,¹⁰ as a result of his experience with the Franklin School, placed great emphasis on the need for meeting the problem of management of these postencephalitic behavior disorders in the community. He wrote, "The strain on the community is unbearable but it is no solution to send these children to a hospital for mental diseases or to a school for feeble-minded where they continue their disorganizing influence." His suggested remedy is to equip a special unit with a specially chosen staff in conjunction with a hospital for the dual purpose of properly treating the individual patient and of protecting the normal children of the community from the influence of those patients who do not improve. It is his contention that the increasingly poor recoveries reported should not permit adoption of an attitude of reconciliation with a hopeless problem, but rather, that they should awaken physicians to realization of distinct responsibilities, inasmuch as the aforementioned poor recoveries concern essentially patients who have not "had adequate treatment, adequate observation or handling except in a most destructive way."

The results of special school projects may be said to be disappointing in terms of actual recovery of patients, but certainly they are favorable in relation to the unsupervised or custodial behavior disorder. In the 1935 report on the Franklin School offered by Bond and Smith, eighty of the eighty-five patients reported showed a tendency toward improvement while they were in the school, but only twenty out of seventy-six satisfactorily maintained that adjustment after return to their homes, the fate of nine patients still in school being undetermined. It must be remembered that these patients represent a rather selective group in that any gross neurologic defect, even if stationary, was sufficient to preclude a patient's admission to the school and that the patients were under the best possible psychiatric supervision while they were in the school.

A colony for children suffering from encephalitic sequelae was established at Kings Park State Hospital in 1924 with facilities for fifty children. In 1929 Gibbs reported that out of 114 patients who had experienced the acute phase at or before the age of fourteen, only seven had been discharged as recovered. Twenty-three were dismissed from the hospital but no comment as to their condition was made and it may be assumed that the recoveries in this group would not remarkably increase the number in the recovery group. Parkinsonism was noted or had developed in fifty-three of these 114 patients, most of whom remained in some hospital because of the incapacitating disease or associated behavior problems.

These statistics provide an idea of the malignant character of the disease. The better recovery figures offered by the studies at the Franklin School may be attributed largely to the exclusion of patients who had parkinsonism and other gross neurologic stigmata whom the Kings Park Hospital admitted to its colony.

Follow-up studies.—A study of fifty-one cases of encephalitic sequelae in which the patients were children was conducted at The Mayo Clinic. This study has been summarized in two reports. The first report was made by R. L. J. Kennedy in 1924. This study was limited to children who had suffered the acute phase of the disease before the age of fifteen and in whom sequelae had been present for from one to five years. For twenty-three patients in whom a personality change of

behavior disorder was evident, the prognosis appeared definitely better than that for the whole group. Excluding from the group any patient who had objective neurologic stigmata, twelve instances of clear-cut behavior disorders remain. Eight of these twelve patients showed trends toward improvement in 1924. In 1939⁴ follow-up data were obtained concerning forty of these fifty-one patients (Fig. 143). One patient had died before publication of the first report. Ten patients could not be satisfactorily traced.

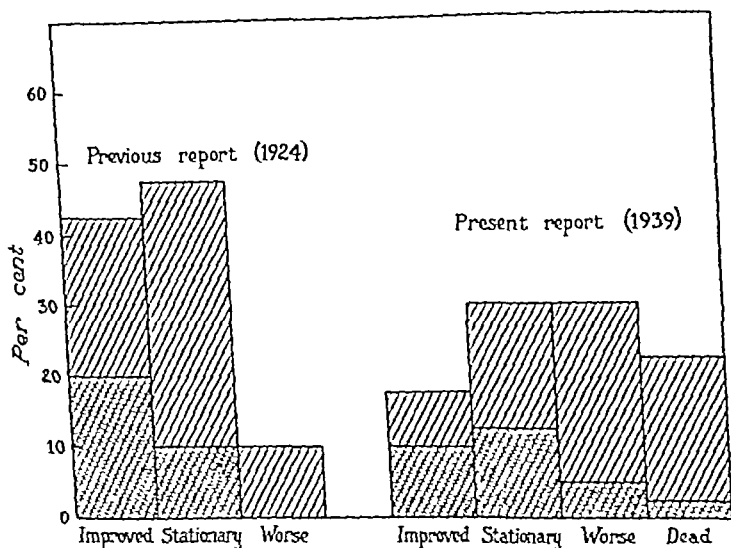


Fig. 143.—Status of forty children with encephalitic sequelae; twelve cases of postencephalitic behavior disorders are included (shown by stippled area).

Of greatest interest were the so-called behavior disorders included in this group of forty patients. Twelve of these patients had conditions so designated in the original report, all of whom were without objective neurologic stigmata. Study of these twelve behavior disorders revealed only four patients as having made a favorable social adjustment. Parkinsonism had appeared in one, grand mal in one, two were in institutions, one was considered an imbecile, one had died of intercurrent infection with some evidence of parkinsonism before death and two had continued as prominent problems of disordered behavior in the community.

W. L. Holt, Jr. in 1937 reported a follow-up study of 266 cases of epidemic encephalitis in which the condition of seventy-one of the patients was classified as behavior disorder at the time of admission. For these seventy-one patients the mean follow-up period was ten years. Forty-three of the seventy-one patients showing behavior disorders had no physical incapacity at the time of their first admission. Five of these forty-three patients recovered, an incidence of 11.6 per cent. To be added to the five patients was an additional group of six patients who were employed and self-supporting, resulting in a total of 25.6 per cent of patients, out of the forty-three who had no physical incapacity, who might be considered to be improved to a fair degree of social recovery. Holt displayed a slightly more optimistic note than other recent commentators, inasmuch as in his opinion a persistent behavior disorder of ten or more years' duration, even if severe enough to require institutionalization, still carries the possibility of social recovery of the patient if neurologic changes have not appeared.

Opposed to this, however, is the potential danger demonstrated by the patient mentioned earlier in this paper (whose condition was presented as evidence for the presence of a chronic encephalitic process), who might have been considered to be recovered ten years after the initial illness, but who presented classical parkinsonism fourteen years after the initial illness.

It is difficult to reconcile the various statistics dealing with recovery, because so many different concepts are implied in the term "recovery." There may be a wide variation between actual, objective recovery and so-called social recovery.

In a discussion of the Kings Park report by Gibbs in 1929, Bond estimated that seven recoveries took place among fifty patients; Bond excluded parkinsonism and any continuing neurologic disorder and arrived at a recovery rate of 14 per cent on the basis of the fifty patients. In 1935 Bond and Smith reported a recovery rate of 26 per cent (twenty out of seventy-six) for patients discharged from the Franklin School who could be considered as having "recovered from the position which they held before the illness."

Adopting such criteria it would seem fair to consider 11.6 per cent (representing five recoveries in forty-three patients) as the true recovery rate in Holt's reported cases.

Further corroborative evidence of the agreement of various investigations is offered by Hohman,⁵ who in 1922 predicted 50 per cent improvement for a group of patients who had post-encephalitic behavior disorders. Recently (1939) Hohman⁶ has reviewed the cases originally reported and has added some others, making a total of twenty-nine cases; only four of the patients have recovered. The recovery rate for this group is 14 per cent, in patients observed for an average of seventeen years and in his opinion this percentage is compatible with the recovery rate to be anticipated in view of the present methods of treatment.

Although the cases of actual behavior disorder in the series which I have reported elsewhere are few, results obtained in that series are in rather close agreement with the results of others. No more than two out of twelve (16.6 per cent) patients who had behavior disorders and on whom I have reported previously should be considered as recovered if the standard of recovery which implies a return of the patient to the position he held before his illness is adhered to.

Probably it is unfair to form any conclusion on the basis of the aforementioned statistics such as the conclusion that the untreated patient who has a postencephalitic behavior disorder shows a recovery rate over a fifteen to twenty-year period of 16 per cent or less, whereas properly supervised patients demonstrate 25 per cent recovery or better.

It is not unfair, however, to call attention to the facts that physicians are likely to become lax in interest in these patients except when an epidemic is concerned; that the social consequences of even a single behavior disorder may seriously disorganize a family or a whole community; that there are sufficient cases in every state even during freedom from epidemics to warrant organization of special units in state hospitals to treat these problems scientifically; and last, that an attitude of hopelessness assumed because of recent studies indicating less favorable prognosis should be superseded by closer observation and study of the entire problem, particularly in regard to the acute and subacute stages of the disease.

Treatment.—Concerning any measures designed to *prevent* sequelae, I have only one suggestion to offer, namely, *rest*. Much has been said about the unfavorable psychologic effects

of long periods of invalidism in children. Rest can become an organized program as well as can the program of school, work, play, and recreation of a normal child. It may require some help from a psychiatrist, an occupational therapist or social worker, depending upon the age of the child, but it can be done very effectively.

General acceptance of the occurrence of damage to the brain, whether the damage is the result of epidemic encephalitis, trauma, or that type of encephalitis which accompanies virus infections of childhood, demands physical rest to enhance the natural forces of rehabilitation of the patient for a number of months following the acute illness. Until physicians are favored with more specific agents of therapy, this general rule of rational management should be exploited to the utmost.

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CERTAIN COMMON TYPES OF LOW BACKACHE: CONSERVATIVE MANAGEMENT WITH SPECIAL REFERENCE TO PHYSICAL THERAPY

FRANK H. KRUSEN AND WILLIAM C. BASOM

It is impossible to discuss all the causes of backache in a presentation of this sort. However, an attempt will be made to present, briefly, the salient diagnostic points and the treatment of some of the common conditions which may produce low back pain.

LUMBOSACRAL ARTHRITIS

Diagnosis.—The patient who has lumbosacral arthritis probably will report a long history of backache which is situated chiefly over the lumbosacral area and may be associated with extension of pain into the thighs. There may be a history of repeated injuries. Palpation and fist percussion will reveal tenderness over the lumbosacral area.

The straight leg-raising test or *Lasègue's sign* will reveal pain in the lumbosacral region and may be associated with pain on both sides. This test is performed in the following manner. With the patient in a supine position, the knee of one extremity is kept straight as the leg is elevated. Limitation of raising and pain indicate a positive *Lasègue sign*.

The "*knee-rocking test*" will also bring about pain with this condition. This test is done with the patient in a supine position by rocking the knees while flexing both thighs passively on the abdomen at the same time.

Forward and backward bending when the patient is in the standing or sitting position will be limited and painful.

Even more help in diagnosis will be obtained by examination of *roentgenograms* which have been centered over the lumbosacral joint (Fig. 144). The views taken should be anteroposterior, lateral and three quarter. The changes most likely to be demonstrated are diminution in the width of the

lumbosacral intervertebral spaces and hypertrophic changes or changes in the articular facets. Macey has stressed the fact that at times, the symptoms may be referable to lesions situated higher up in the spinal column. Therefore, if nothing is revealed in the pictures of the lower portion of the spinal col-

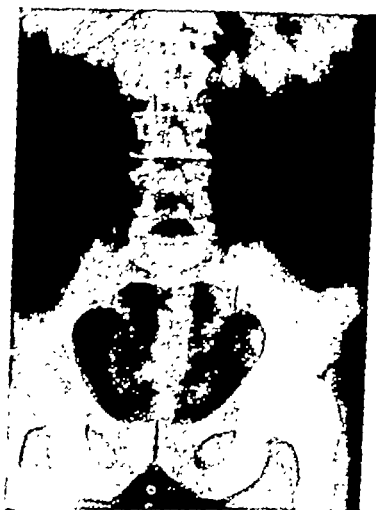


Fig. 144.—Lumbosacral arthritis.

umn, roentgen-ray photographs of a higher level of the spine may reveal lesions which might otherwise have been overlooked.

TREATMENT.—Treatment is discussed under “sacro-iliac arthritis.”

SACRO-ILIAC ARTHRITIS

Diagnosis.—*Tenderness* is the most constant sign in pathologic conditions of the sacro-iliac region. Pressure on the adjacent ilium just above the sciatic notch is most likely to elicit this sign. Pressure can be made directly over the joint during a rectal examination. Ghormley has emphasized the fact that on pressure, tenderness which is found consistently over the same points is a most important sign in sacro-iliac arthritis and aids in differentiating the condition from lumbosacral arthritis.

When a patient has sacro-iliac arthritis, motion of the spinal column, such as forward bending, which is usually

limited in the standing position, is not limited in the sitting position. In the latter position, most of the spinal motion occurs in the lumbar portion of the spinal column.

There is no pain when the "*knee-rocking test*" is used.

Gaenslen's sign will demonstrate which side is affected and will rule out lumbosacral arthritis. This test is performed as follows: The patient is in a supine position. His left side, for example, is close to the edge of the table. The right knee and hip are flexed against the abdomen and held there by the patient's clasped hands over the knee. The examiner assists by

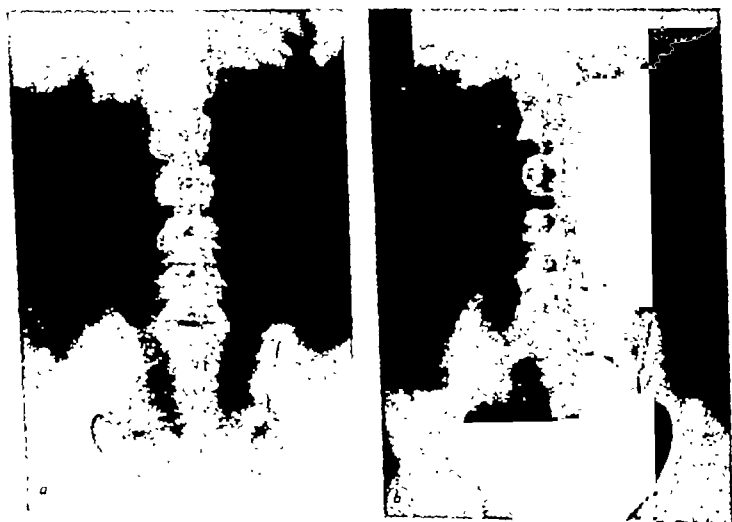


Fig. 145.—Sacro-iliac arthritis; *a*, before fusion; *b*, after fusion.

placing his hand also on the right knee. The left thigh is placed off the side of the table and the free hand of the examiner is used to exert force in hyperextending the left hip of the patient. If the left sacro-iliac joint is involved, pain should be elicited in that region. The right sacro-iliac joint is examined by reversing the position. In this test the lumbosacral joint is fixed and the force is exerted mainly on the sacro-iliac joint.

Attempts at straight leg-raising (*Lasègue's sign*) may indicate limitation of motion.

Roentgen-ray photographs (Fig. 145 *a* and *b*) are not of so

much help in the diagnosis of this condition as they are in the diagnosis of lumbosacral arthritis. Localized and stereoscopic views are of greatest value. Fusion, variations in the width of the joint (which are not very important), marginal hypertrophic changes or destructive changes, may be demonstrated.

The infectious type of arthritis is usually accompanied by more *spasm* of the muscles than is the hypertrophic type. The presence of infectious arthritis is suggested by a history of pain occurring after resting and of pain and stiffness occurring



Fig. 146.—Radiant heat lamp containing a 250 watt CX bulb which is very satisfactory for local applications of heat to the back.

on arising in the morning. The presence of the hypertrophic or traumatic type of arthritis is indicated by a history of pain that is aggravated by work.

Treatment.—The conservative treatment is similar in both infectious (atrophic) and senescent (hypertrophic) arthritis of either the lumbosacral or sacro-iliac joints. The patients should have rest in bed on a firm mattress without inner springs. Boards should be placed between the mattress and the bed springs. The pelvis may be fixed with adhesive tape

which is applied in strips 2 inches (5 cm.) wide from trochanter to trochanter across the back, and from 1 inch (2.5 cm.) below the top of the gluteal clefts upward well into the lower thoracic part of the back. A scultetus binder also may be used.

The lumbar portion of the spinal column may need some sort of support. For this purpose a blanket may be rolled up and employed according to the patient's tolerance.

Usually, traction is necessary and may be applied to each leg with padded ankle cuffs or adhesive tape. Six to 10 pounds (2.7 to 4.5 kg.) on each leg are used intermittently throughout the day.

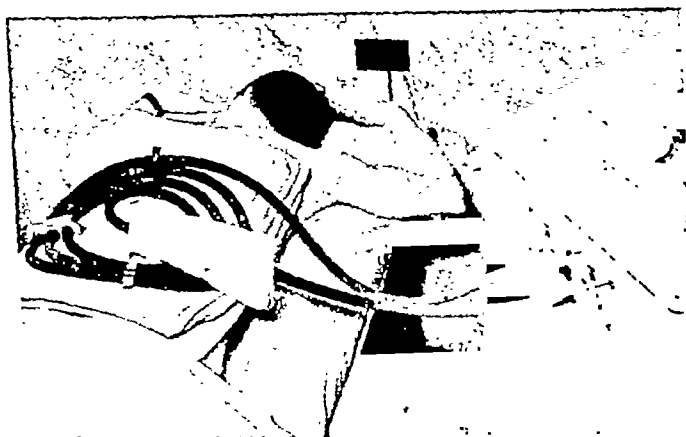


Fig. 147.—Application of short-wave diathermy to the lower portion of the back by means of an electric "pancake coil."

Applications of radiant heat and massage are alternated daily with local applications of diathermy and massage. Heat may be applied by means of a 250 watt infra-red bulb in a small cup-shaped reflector (Fig. 146). This is placed about 18 inches (46 cm.) above the back of the patient for about thirty minutes, or short-wave diathermy, preferably applied by means of "pancake coil," may be employed (Fig. 147). Sedative massage then follows for about fifteen minutes.

There may be muscle spasm and also a list of the spinal column, which is usually away from the side affected (sciatic scoliosis) in the severe instances. In such cases manipulation with or without anesthesia may be used. However, Henderson

has pointed out that peroneal paralysis or avulsion of the intervertebral disk may result from such manipulation. Thus, this procedure may prove to be dangerous and should be used only in carefully selected instances.

Acute radiating pain sometimes may be relieved by stretching of the hamstring muscles while the patient is under the influence of general or spinal anesthesia. Following this, benefit may be obtained by immobilization with a hip spica cast. Some help may be obtained from an injection of procaine into the epidural space.

As a result of conservative treatment as first outlined, the maximal benefit should be obtained in ten to fourteen days. After this a supportive corset or belt is indicated. Men will usually wear the heavy belt, whereas women prefer a corset. Most important is the fitting rather than the type.

Conservative therapy should relieve most of the patients suffering from backache caused by arthritis of the lumbosacral or sacro-iliac joints.

If operative procedures have to be used, it should be definitely established which joint is involved.

Statistics concerning the relative merits of conservative versus surgical treatment are difficult to obtain.

POSTURAL STRAIN

Diagnosis.—Postural strain may often be observed: (1) in large heavy persons with heavy abdomens which cause a constant drag on the ligaments thus producing the symptoms of postural strain, (2) in thin persons with poor musculature who stand with round shoulders and marked lordosis, (3) in those who have the round back of adolescence, and (4) in those who have various conditions in which faulty posture may play a part (Fig. 148). Many backaches are relieved when the strain of standing is removed.

Treatment.—When there is severe pain, conservative therapy, such as is administered for lumbosacral and sacro-iliac arthritis, should be used.

Postural training is most important. The individual should be shown how to assume correct posture. Usually, the patient exhibits a tendency toward increased lumbar lordosis and dorsal kyphosis.

Patients respond best and correct these curvatures more easily if they follow the advice to "push the top of the head up." The lumbar curve may be reduced with abdominal muscle exercises. Exercises in the prone position, such as raising of the upper part of the trunk and head without assistance of the upper extremities, will help straighten the dorsal curve.

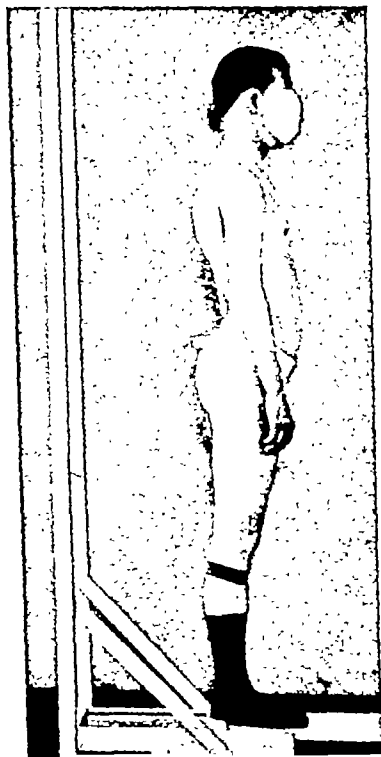


Fig. 148.—Faulty posture causing backache as a result of postural strain.

The patient should at all times remind himself to keep the spinal column straight. Constant daily self-correction over a long period should bring about satisfactory improvement.

SPONDYLITIS DEFORMANS

Diagnosis.—This disease is recognized by the following:
 (1) Early rigidity of the spinal column is observed by having

the undraped patient bend forward and from side to side while standing with the hands back of the head. (2) The decreased thoracic expansion is demonstrated by placing a tape measure around the chest at the level of the nipples. The patient exhales completely. Expansion is measured when the following inhalation is complete. As a rule, in this condition the usual measurement of 3 to 4 inches (8 to 10 cm.) is found to be reduced to only 1 inch (2.5 cm.) or even less. (3) Calcification of the ligaments or fusion of the sacro-iliac joints will be demonstrated in the roentgenograms (Fig. 149a).



Fig. 149.—*a*, Spondylitis deformans; *b*, senile osteoporosis.

Treatment.—Foci of infection should be searched for and, if found, eliminated if it is practicable to do so. The prevention of deformity is the most important point in management. Rest in bed is best during the painful stage. Careful observation should be maintained constantly to avoid the development of kyphosis. A Whitman frame or something similar may have to be used for this purpose.

The spinal column should be supported, when the patient begins to stand, by means of a strong, well-fitting brace with shoulder straps. Physical treatment, such as diathermy or radiant heat followed by massage and postural exercises, should

be employed daily for a long time. Deep breathing exercises should be used to attempt an increase in thoracic expansion. Head traction followed by the application of a Thomas collar may be necessary if the cervical portion of the spinal column is involved.

OBER'S DISEASE OR CONTRACTED ILIOTIBIAL BANDS

Ober has found that contracted iliotibial bands may be associated with some instances of low back pain, frequently with sciatica. There will be a lateral deviation of the spinal column to the affected side if the condition is unilateral. A lumbosacral strain will result if the condition is bilateral.

Diagnosis.—In attempting to establish the diagnosis the physician should employ *Ober's test*, which he has described as follows: (1) The patient lies on his side on a table, the shoulders and pelvis being perpendicular to the table. (2) The leg on which he is lying is flexed at the knee, and the hip is flexed and kept flexed to flatten the lumbar curve. (3) If the patient is on his left side, the examiner (standing behind him) places his left hand over the patient's hip in the region of the trochanter to steady him. (4) The right leg is flexed to a right angle at the knee, and is grasped just below the knee with the examiner's right hand, the leg and ankle being allowed to extend backward under his forearm and elbow. (5) The right thigh is abducted widely and hyperextended in the abducted position, the lower part of the leg being kept level and care being taken to keep the hip joint in a neutral position as far as rotation is concerned. (6) The examiner slides his right hand backward along the patient's leg until it grasps the ankle lightly, but with enough tension to keep the hip from flexing. (7) The thigh is allowed to drop toward the table in this plane. If the fascia lata and iliotibial band are tight, the leg will remain more or less permanently abducted.

Treatment.—The treatment at first may be *conservative*. An attempt may be made to stretch the bands by active and certain forcible passive exercises and postural exercises.

A special form of adhesive strapping may be tried. The patient lies on his side on the table with his hips and knees flexed. The thighs are maintained in an abducted position by pillows between the knees. Tape in long strips is applied

from a point just above the knee on the lateral aspect of the affected thigh up across the iliac crest and lower back to the opposite side. A second transverse layer is applied. Then a longitudinal layer is added. This helps relieve tension on the tight band.

If this procedure does not help, Ober recommends his *fasciotomy*. The incision is made from just below the iliac crest to the trochanter. The fascia is exposed from the anterior superior iliac spine back to the edges of the gluteus maximus muscle. The fascia is divided transversely at its region of greatest contracture, which is from the anterior to the posterior landmarks.

SENILE OSTEOPOROSIS

This condition occurs among patients who are usually more than fifty years of age and who are always more than forty years of age. Evidence of senility, general atrophy of tissue and arteriosclerosis may be found. Severe disabling pains in the spinal column, and kyphosis referable to extensive changes in the vertebrae and intervertebral disks observable in the roentgenogram comprise the syndrome.

The *diagnosis* can be established by the roentgenologic findings (Fig. 149*b*) even in the absence of signs and symptoms. The laboratory findings in general are negative.

Treatment.—Pain must be relieved; further deformity must be prevented and bone recalcification must be promoted.

Rest in bed may be the only recourse for relief of severe pain. Since old people do not tolerate rest in bed well, this should be discontinued as soon as possible. When the patient is ambulant, a corset with steel stays usually gives enough support. These patients do not endure braces well, because many have only a thin covering of skin over their bony prominences. However, a brace may save the patient from falling victim to a fracture or additional deformity.

Physical therapy, such as applications of heat, massage to increase local circulation and sun baths or artificial ultraviolet irradiation to promote absorption of calcium, are very helpful.

The diet should be well balanced. Many of these patients are undernourished and anemic. The diet should be arranged to combat these conditions as well as to maintain good general health.

Evidence points to the suggestion that a deficiency of calcium in the diet may be one factor in producing senile osteoporosis. A teaspoonful of tribasic calcium phosphate, taken three times a day, is therefore valuable. Also, vitamin D should be administered in adequate dosage.

In many cases the period required for recalcification and true recovery may extend beyond the patient's period of life expectancy. In all cases, the period of treatment is long.

The combination of braces, tribasic calcium phosphate and cod liver oil soon becomes very tiresome to these patients. Temporary symptomatic improvement may tend to encourage them to discontinue the therapy prematurely. It should be impressed on the patients that treatment must extend over a long period if it is to be adequate.

POSTERIOR PROTRUSION OF INTERVERTEBRAL DISK

Diagnosis.—The usual symptom is intermittent root pain, often unilateral, sharp and shooting, usually in the sciatic

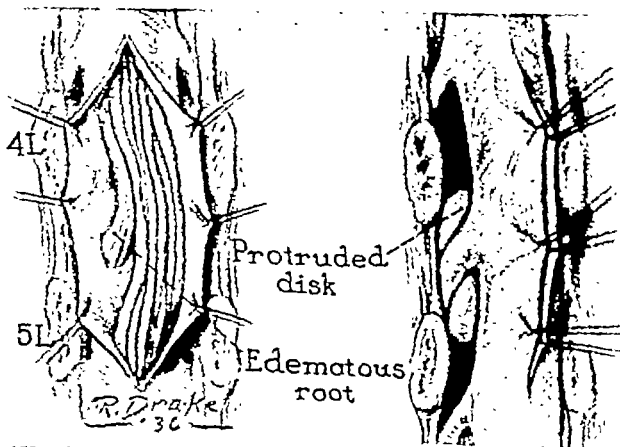


Fig. 150.—Appearance at time of operation of a protruded intervertebral disk (after Love and Camp).

nerve and often described as being "like an electric shock." The pain is aggravated by coughing, jarring or sneezing. It may be precipitated by tension on the involved nerve. Numbness and weakness occasionally may be present.

The *Lasègue sign* may be positive, the Achilles-tendon reflexes diminished, the sciatic or other nerve roots tender, total protein content of the cerebrospinal fluid increased, or the protruded disk visualized in the roentgenogram following injection of air or iodized oil into the intraspinal subarachnoid space. All these signs may be present in other conditions. The appearance of the lesion at the time of operation is illustrated (Fig. 150).

Treatment.—If the patient is not relieved by conservative treatment and if neurologic and roentgenologic studies reveal a protruded disk, the disk should be removed surgically. If operation is refused, local applications of radiant heat, followed by sedative massage and the employment of a suitable spinal brace may give considerable symptomatic relief. It should be remembered that flexion of the spinal column *may* cause a protruded disk to be drawn back into the intervertebral space, whereas hyperextension of the spinal column may cause increased protrusion of the disk. Relief might follow manipulation of any sort, but such a procedure is dangerous and can produce no permanent benefit.

SPONDYLOLISTHESIS

Diagnosis.—Meyerding has pointed out that the *symptoms* are pain, stiffness and weakness in the lower part of the back, sacro-iliac region, hips and legs. Relief is achieved by recumbency. Ten per cent of patients have no symptoms. This condition consists of a forward and downward lumbosacral or lumbar vertebral subluxation. In advanced instances there may be a transverse groove in the lumbar part of the spinal column, shortened torso, abdominal crease, and lordosis associated with spasm and prominence of the erector spinae muscles (Fig. 151). The *roentgenograms* reveal the defect between the body and neural arch of the vertebra. Displacement is revealed clearly in the lateral view.

Treatment.—For symptomless patients (10 per cent) observation only is required. In 12 per cent of Meyerding's cases spinal fusion has been done and the procedure is indicated in a still higher percentage of cases. In the other 73 per cent in which symptoms are mild or in which the patient refuses surgical intervention, conservative treatment is required. Trac-

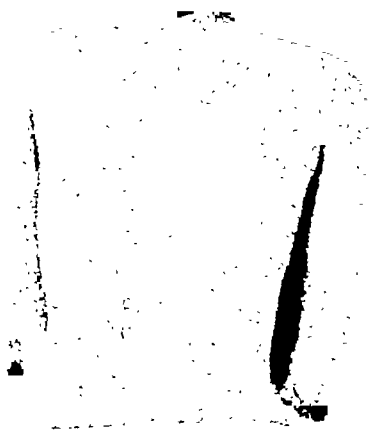


Fig. 151.—Appearance of the back in the presence of spondylolisthesis, showing the grooved lumbar position of the spinal column and prominence of the erector spinae muscles (courtesy of Dr. H. W. Meyerding).

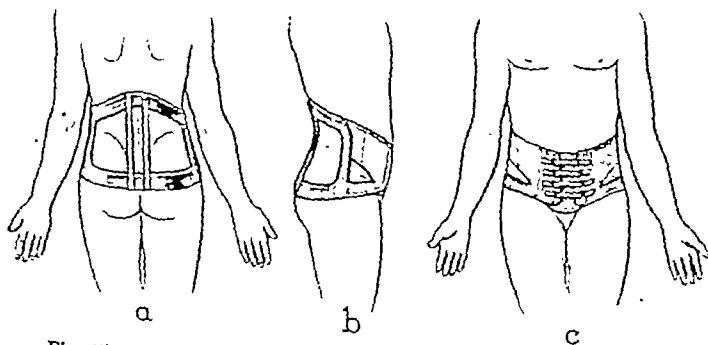


Fig. 152.—A “rocking chair belt” which may be employed for support of the spinal column in spondylolisthesis (courtesy of Drs. H. W. Meyerding and G. A. Pollock).

tion may be used to attempt reduction of the deformity and a plaster cast may be used for fixation. A “rocking chair belt” (Fig. 152) may be used for support. Radiant infra-red heat

heat and *very firm* massage applied directly to the indurations and stretching exercises are indicated. Ordinary massage is of little value. If symptoms persist, treatment should continue for many weeks. Adequate rest should be obtained. In some

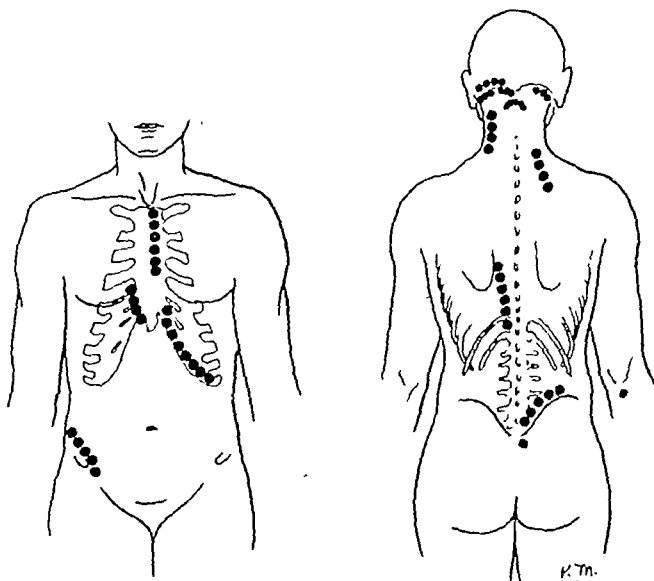


Fig. 154.—Common situations of nodules in fibrositis (courtesy of Dr. C. H. Slocumb).

instances, Rosenow's fibrositis vaccine seems beneficial, and it may be administered in conjunction with other forms of treatment.

SUMMARY AND CONCLUSIONS

In the presence of lumbosacral or sacro-iliac arthritis, postural back strain, spondylitis deformans, contracted iliotibial fasciae, senile osteoporosis, posterior protrusion of intervertebral disks, spondylolisthesis, coccygodynia, or fibrositis there may be more or less severe pain in the lower part of the back.

In the majority of these conditions conservative treatment may be employed to great advantage. In certain conditions, such as arthritis of one or more joints of the lower part of the back, postural strain, osteoporosis, or fibrositis, physical therapy will usually suffice to relieve the patient of the back-ache. In other lesions, such as posterior protrusion of an

intervertebral disk or spondylolisthesis, conservative treatment should play a *secondary* rôle. Surgical intervention is usually of primary importance in these two conditions. The protruded disk should be removed surgically and in the presence of advanced spondylolisthesis the spinal column should be fused. If, however, surgical operation is refused or is contraindicated for some reason, use of physical treatment and other conservative measures may benefit the patient greatly.

In the majority of instances of contracted iliotibial fascia and coccygodynia, conservative treatment should be tried first for a prolonged period, ranging up to six months. If, after a thorough trial of physical treatment, as previously described, there has been no relief of the backache and other symptoms, then surgical intervention should be considered. Fasciotomy may be performed for the eradication of contraction of the iliotibial bands and coccygeal resection for relief of coccygodynia. In these cases, however, surgical treatment usually may be regarded as a secondary consideration.

In any instance of low backache the diagnosis must be *clearly established* before treatment is inaugurated. In the ten relatively common conditions which we have mentioned, physical treatment may play an important rôle in bringing surcease from low back pain and discomfort. In all but four of these ten conditions conservative treatment, especially physical therapy, is the primary consideration and is usually the only treatment necessary. In two of the lesions mentioned (namely, contracted iliotibial bands and coccygodynia) conservative management by physical treatment should be attempted first and if it fails, the physician may resort to surgical procedures.

In the other two conditions which we have discussed (namely, posterior protrusion of intervertebral disks and spondylolisthesis) surgical operation should be considered as soon as the diagnosis is established, because there is little hope of obtaining by any other means the complete and immediate relief of symptoms which an operation may produce.

When logically applied in conjunction with other forms of treatment as indicated, *radiant heat*, *diathermy*, various types of *massage*, and specific methods of *exercise* will be found to be very effective in the treatment of many varieties of low backache.

THE ADVANTAGES OF HEPATIC INJURY AND JAUNDICE IN CERTAIN CONDITIONS, NOTABLY THE RHEUMATIC DISEASES

PHILIP S. HENCH

INTRODUCTION

Until recently jaundice has been considered an enemy to health, or at least a nuisance to mankind. It certainly has not been looked on as a friend to the sick. Recent investigations, however, indicate that hepatic injury associated with jaundice may be distinctly advantageous to persons with certain conditions against which they exert a neutralizing effect. Consequently efforts are being made to apply this clinical antagonism to the field of therapy. It is the purpose of this paper to evaluate these efforts and to determine how practical they are to date.

From the time of Hippocrates observations have been made in the curative effects, real or supposed, which some diseases exert on others.^{3, 18, 19, 60} But the observations made of any one clinical antagonism generally have been few, and many supposed examples have been described in such meager detail that reports thereon constitute little more than hearsay. Few also have been the attempts to make practical use of these antagonisms. A notable example was the use of malarial fever in cases of general paresis.

CONDITIONS ANTAGONISTIC TO RHEUMATISM

Comments on conditions supposedly antagonistic to any of the rheumatic diseases are difficult to find, but three old and two recent examples may be noted. In 1898 Campbell, discussing the beneficial effects of one disease on another, cited briefly three cases of "chronic rheumatism" of many years' duration; one patient was "cured" by typhoid fever, and another after amputation of the legs necessitated by an accident.

The third case was that of a "martyr to chronic rheumatism" in which malignant disease of the liver developed. It was not noted whether jaundice was present or not, but "ever after all signs of joint trouble completely disappeared." In 1920 Pemberton⁶¹ wrote: "Any critical observer can satisfy himself that the incidence of some conditions, . . . such as pneumonia and pregnancy, may be followed by temporary improvement or entire surcease of symptoms in chronic arthritis." In 1934 Fox and Van Breemen wrote: "A phenomenon of general pathological significance, which should certainly be investigated farther, is that some infectious illnesses, such as influenza and scarlatina, nearly always aggravate existing rheumatism or excite rheumatism; whereas after some other infectious diseases, such as typhoid and diphtheria, we have observed striking improvements in chronic rheumatism. This may contain the key to therapeutical possibilities."

ANTAGONISTIC EFFECTS OF HEPATITIS AND JAUNDICE

Historical.—A striking example of clinical antagonism came to my attention in 1929 and concerned the ameliorating effect of hepatitis and jaundice in cases of chronic infectious (atrophic, rheumatoid) arthritis and primary fibrositis. This phenomenon I²⁴ described in detail in 1933 and subsequently, but like most original ideas my description represented, not a discovery, but a rediscovery of a completely forgotten phenomenon which had been noted casually years previously. Still, in 1897, described the disease which has come to bear his name. Buried in this classic is this sentence: "Curiously enough, some accidental complications have been followed by marked improvement; thus I have known measles, scarlet fever, and catarrhal jaundice to be each followed by distinct improvement of the joint symptoms." In contrast to Fox and Van Breemen, Still considered intercurrent scarlet fever of possible benefit, rather than harm.

Even more pertinent were the brief remarks sent by Wishart in 1903 to the editor of the "British Medical Journal." They are worth repeating in full:

"When jaundice of an obstructive type becomes fully established in the system of a patient suffering from chronic rheumatism, rheumatoid arthritis, or muscular rheumatism, the pains characteristic of these diseases disappear en-

tirely. Such at least has been my experience in four cases which have come under my observation during the past eight months. The jaundice persisted in three of the cases during the short time they were under my observation. The fourth case is that of a coalminer aged 40 years. He had been subject to attacks of muscular rheumatism at various intervals during the past eight years. Six weeks ago he was confined to bed with a severe attack of gastrointestinal influenza. On the eighth day jaundice appeared as a complication, but gradually disappeared during the succeeding fourteen days, by which time his general condition was materially improved. On the day after that on which the jaundice had disappeared muscular rheumatism set in as a sequela, and still remains very persistent.

"One may therefore conclude from the facts observed in the four cases mentioned above that the bile present in the circulation had the effect of entirely overcoming the muscular and joint pains temporarily. The exact way in which this result was attained is difficult to explain, but it may be noted that sodium salicylate which, when administered alone, has little or no effect on chronic rheumatism, is the only drug that has been proved actually to produce an increased flow of bile."

These comments by Still and Wishart failed to attract the attention of the clinicians of that day and were not quoted in texts or elsewhere in the literature on rheumatic diseases so far as I can determine. I have found four other casual references to this phenomenon in more recent literature. In 1920 Pemberton⁵⁰ reported a case of arthritis (case 53) in which acute catarrhal jaundice developed: "During ten days of extremely low diet, necessitated by nausea, her joint condition entirely cleared up and remained so until she again was eating as before." Pemberton^{50, 52} ascribed the relief, not to the jaundice, but to the dietary restrictions incident to jaundice. In 1932 Parsons and Harding⁴⁷ reported that jaundice developed after one of their patients had taken cinchophen for her "rheumatism"; "though [the tablets] made her dizzy the 'rheumatism' disappeared." In another report Parsons and Harding⁴⁶ also stated: "A history of the taking of cinchophen followed by the disappearance of pain associated with the onset of jaundice is usually obtained." In 1933 Grigg and Jacobsen, writing not on arthritis but on cinchophen toxicity, noted the case of a woman with arthritis of many years' duration in which fatal cinchophen toxicity with jaundice developed. It was stated: "It is worthy of note that after the appearance of the jaundice she had no subjective symptoms of arthritis." These various remarks also were made without further comment; it

appears that the possible significance of this phenomenon was not fully appreciated.

Author's experience.—Between 1929 and 1938 I noted the ameliorating effect of various types of jaundice on forty-five patients: twenty-eight with chronic infectious arthritis, twelve with primary fibrositis, four with sciatic pain and one with hypertrophic arthritis. Details regarding these cases (two series) have been reported.²⁴⁻²⁷

In the twenty-eight cases of *chronic infectious arthritis*, the average duration of arthritis was about 5.3 years; spontaneous intrahepatic or catarrhal jaundice occurred in fifteen, and obstructive jaundice from stones in two. The duration of jaundice varied considerably, but averaged about eight weeks. Coincident with the development of jaundice, remissions in articular symptoms occurred and lasted from one and a half to eighty-two weeks. Relief of articular pain was complete in nineteen, or 68 per cent, almost complete in nine, or 32 per cent. Active articular swelling, muscular stiffness, soreness and fatigue also were reduced markedly or disappeared, but residual articular thickening and stiffness from deformity were, of course, unaffected. In the few fatal cases of "cinchophen jaundice" relief, generally complete, lasted till death. In practically all the others articular symptoms eventually returned, frequently in milder form, but generally in the same form as before the jaundice.

The twelve patients with *primary fibrositis* (average duration 4.7 years) were affected thus: nine with intrahepatic (cinchophen) jaundice, two with obstructive jaundice from stones, and one patient with an obstructive jaundice from carcinoma of the ampulla of Vater. Jaundice lasted an average of about 5.7 weeks; with its onset symptoms of the fibrositis disappeared completely in all twelve cases and remained absent for from four to 104 weeks. Thereafter symptoms generally returned; sometimes they were as severe as before, at other times, of lesser degree.

In the four cases of *sciatica*, the sciatic pain was associated, in one case each, with primary fibrositis, with pelvic malignancy, with spondylitis and with lumbosacral hypertrophic arthritis. Intrahepatic jaundice developed, in three cases from cinchophen, once after the use of some patent medicine. With

the onset of jaundice the sciatic pains disappeared for some weeks or months.

A man, aged forty-nine years, for six years had a painful hip and thigh from hypertrophic arthritis with an Otto pelvis (protrusion of femoral head into the acetabulum); catarrhal jaundice developed and persisted for three weeks, during which time relief from articular symptoms was complete at first and later notable but incomplete.

The duration and completeness of these remissions bore a general, but not a specific, relationship to the duration and intensity of the jaundice. The length of remissions varied considerably but averaged about twice that of the jaundice. Mild jaundice generally was ineffective; some of the patients with chronic infectious arthritis were not relieved by slight jaundice in which concentrations of bilirubin were less than 5 mg. per 100 c.c. of serum. The zone of therapeutic effectiveness seemed to begin when the concentration of bilirubin was about 8 mg. per 100 c.c. of serum. When the relief appeared, usually it was delightfully obvious to the patients and evoked such comments as, "When the jaundice came in the front door, the rheumatism went out the back door."

CONFIRMATORY OBSERVATIONS

A number of other physicians have since noted this phenomenon in a total of twenty-seven cases of chronic infectious arthritis, psoriatic arthritis, hypertrophic arthritis, intramuscular and periarticular fibrositis, and sciatica (Tabulation)* 2, 5, 9, 10, 12, 21, 35-37, 56, 63, 68-70, 75. Among twenty-nine cases there were only two, Thompson and Wyatt's⁷⁵ case 2 and Lichtman's³⁰ case 5, in which jaundice (degree unstated in one case, "latent" in the other) was not associated with some relief of articular pain.

Jaundice and chronic infectious (atrophic) arthritis.—Fifteen patients with this disease noted marked amelioration of articular symptoms with the onset of several types of intrahepatic jaundice. In most cases relief of articular pain was complete; in some reduction of swelling also was seen and in at

* An additional number of observations have been sent to me by several physicians who noted the phenomenon in one or more cases each, the data thereon being so far unpublished.

least two there was complete disappearance of all articular pain and swelling. In five cases the relief of pain was reported as incomplete but marked, for pain practically disappeared and improvement was dramatic. The remissions lasted from thirty days to two years. Then the pain returned; sometimes it was as severe as before, but usually it was much less intense, or considerably less severe. One patient was fairly free of pain for three years before her disease became bad again. In three cases symptoms had not returned up to the time the cases were reported five months, one year and more than two years after relief began.

Jaundice and psoriatic arthritis.—One of Sidel's^{68, 70} patients had psoriatic arthritis: generalized psoriasis with an associated chronic arthritis affecting many joints, including the distal interphalangeal joints.^{69b} With the onset of a fairly intense catarrhal jaundice articular pain disappeared completely and articular redness and swelling were distinctly lessened. The jaundice did not affect the psoriasis. Bauer^{6a} noted a case of chronic polyarthritis with psoriasis in which cinchophen toxicity induced a complete remission of the arthritis but not of the psoriasis. But it was considered to be a case of atrophic arthritis with coincidental psoriasis rather than one of true psoriatic arthritis.^{5b}

Jaundice and hypertrophic arthritis.—It is not clear to what extent jaundice may affect primary hypertrophic (senescent, osteo-) arthritis or secondary hypertrophic arthritis. Two of Sidel's patients^{60a} with osteo-arthritis noted only slight improvement during obstructive jaundice from pancreatic carcinoma. Burt's patient with osteo-arthritis said that jaundice cured her rheumatism but no details were given. Articular relief was noted by one of my patients, aged forty-four years, with lumbosacral and sciatic pain and hypertrophic changes in lumbar facets, and by another, aged forty-nine years, with marked hypertrophic arthritis of both hips and Otto pelvis, but they probably had secondary, not primary, hypertrophic arthritis.²⁷ One of Parsons and Harding's⁴⁷ patients may or may not have had primary hypertrophic arthritis; she was a woman, aged sixty-four years, who had "rheumatism" in one knee.

Jaundice and fibrositis (intramuscular and periarthicular).—Borman's first case was one of diffuse myofibrositis

and peri-arthritis. It is difficult to classify the case of Boros in which "rheumatic pains" had been present for more than ten months or the second case of Ahlberg in which "rheumatism" in legs, knees, ankles and shoulder had been present for fifteen to twenty years, but I have listed them as probable cases of fibrositis, not arthritis. Lichtman's³⁷ case was labeled "rheumatoid arthritis" and I have so listed it although roentgenograms of knees did not reveal changes after ten years of painful knees.

Jaundice and sciatica.—To my cases of sciatica relieved by jaundice Lichtman³⁸ has added four of sciatic neuritis in which the sciatica preceded the symptoms of hepatitis; when jaundice accompanied the hepatitis, the sciatic pain was notably or completely relieved. In a fifth case sciatic pain and "latent jaundice" (icterus index 15; serum bilirubin 0.6 mg. per 100 c.c.) subsided simultaneously.

Jaundice and rheumatic fever.—Veil saw a patient aged seventeen years who had severe laryngitis, then meningitis and "acute rheumatic fever" which were followed by jaundice. The temperature fell as the jaundice progressed, the course of the disease lasting about four weeks. In one of my cases^{27a} jaundice of uncertain intensity developed during the silent or prodromal phase of rheumatic fever; four days after the jaundice disappeared an acute rheumatic attack occurred; obviously the jaundice did not abort it. These cases do not permit conclusions as to the effect of jaundice on rheumatic fever. However, a physician⁷¹ recently wrote me of a patient with "rheumatic fever who had had repeated exacerbations of acute arthritis"; she became jaundiced (icterus index 34.4) and "with the onset of the jaundice, in spite of the presence of fever, she has had no further pain in her joints. The fever lasted the usual length of time."

TYPES OF JAUNDICE ASSOCIATED WITH THE PHENOMENON

Adding my forty-five cases to the twenty-seven noted by others (Tabulation), I find that seventy-two cases of effective jaundice have been reported. The various types of jaundice were as follows: thirty-two cases of cinchophen jaundice, twenty-two of spontaneous, nonfatal, intrahepatic (catarrhal, infectious, idiopathic) jaundice, four of obstructive jaundice

TABULATION

EFFECT OF JAUNDICE ON ARTHRITIS, FIBROSITIS AND SCIATICA: SYNOPSIS OF RECENT REPORTS (RELIEF IN 27 OF 29 CASES)

Worker and date of publication.	Cases.		Jaundice.			Remission Induced.		Outcome; comment. Condition after remission.
	Condition.	Duration, yrs.	Type.	Intensity.	Duration, wks.	Degree of relief.	Duration, yrs.	
Sidel, 1933. Sidel and Abrams, 1934.	1. Psoriatic arthritis.	5	Catarhal.	"Fairly intense."	5	Complete relief of pain. Redness and swelling distinctly lessened.	Several weeks.	Joint pains "much milder." Psoriasis unaffected by jaundice.
	2. Chronic infectious arthritis.	3	Cinchophen hepatitis.	Icterus index, 132.	5	Complete relief of pain.	2	Much less intense.
	3. Chronic infectious arthritis.	1/4	Catarhal.	Icterus index, 55.	31 + days.	Complete relief of pain.	31 + days.	Considerably less severe.
	4. Chronic infectious arthritis (monarthritic).	1/4	Cinchophen hepatitis.	"Intense."	8 +	Complete relief of pain.	2 +	No return of arthritis to date of publication.
Haden, 1933.	Chronic infectious arthritis.	•	Hepatitis from neoarsphenamine.	•	•	Complete relief of pain.	1 +	No return of arthritis to date of publication.
Borman, 1936.	1. Fibrositis, periarthicular and intramuscular.	1	Catarhal.	S. B. R. t, 20 mg.	•	Distinct but incomplete relief of pain.	•	2 years later, only slight aching.
	2 "Chronic, periarthritic" (probably infectious arthritis "asiform finger joints").	2	Catarhal.	S. B. R. t, 25 mg.	19 days.	Notable but incomplete reduction of pain and swelling.	•	•
Doros, 1937.	"Rheumatic pains."	10 + mo.	Cinchophen hepatitis.	Icterus index, 250.	14	"All rheumatic symptoms cleared up" (all so named hay fever).	1 +	No return of rheumatic symptoms or of hay fever to date of publication.

1. Sciatic neuritis.	$\frac{1}{2}$	Spontaneous subacute liver atrophy.	.	.	4+	Notable but incomplete relief of pain.	.	Death.
2. Sciatica.	3 wks.	Catarhal.	.	.	.	Apparently complete relief of pain.	.	1 years later; no return of sciatica to date of publication.
3. Sciatica.	2	Acute hepatitis; chronic cirrhosis.	.	.	.	Sciatic pain subsided.	.	Sciatica returned after acute phase of hepatitis subsided.
4. Sciatica.	8 wks.	Probable catarhal (5 grains cinchophen).	.	.	.	Sciatic pain definitely subsided.	.	Death from subacute liver atrophy.
5. Sciatic neuritis, onset recent.	.	Latent jaundice, intra-hepatic (?).	.	.	2+	Apparently no relief of sciatica during latent jaundice. Pain and jaundice subsided simultaneously.	.	Apparently no recurrence of pain to date of publication.
"Rheumatoid arthritis" and alcoholic polyneuritis.	2 wks.	"Emotional jaundice" (spontaneous onset 1 hour after seeing son killed).	.	.	About 6.	Complete disappearance of all joint pain and swelling, but neuritic pains unaffected.	$\frac{1}{2}+$	No return of arthritis to date of publication.
1. Chronic infectious arthritis.	.	Cinchophen hepatitis.	S. B. R.†, 24 mg.	30 days.	.	Joints "entirely leveled."	30 days.	Joints "fairly free for 3 years"; then return of severe arthritis.
2. Chronic infectious arthritis.	.	Cinchophen hepatitis.	S. B. R.† not known.	.	No relief.	.	.	.
3. Chronic infectious arthritis.	$\frac{2}{3}$	Post-transfusion jaundice (chills, emesis, hemolytic anemia, hemoglobinuria).	S. B. R.†, 12 mg.	5 days (severe but abort).	Complete relief of joint pains and swellings.	.	1 $\frac{1}{2}$	Leaves severe after 16 months.
1. Osteo-arthritis.	.	Obstructive from carcinoma of pancreas.	.	.	Slight relief of joint pains.	.	.	.
2. Osteo-arthritis.	.	Obstructive from carcinoma of pancreas.	.	.	Slight relief of joint pains.	.	.	.

Rule-Moreno and Caruso, 1938.

Thompson and Wyatt, 1938.

Leitman, 1938.

TABULATION (Continued)

Worker and date of publication.	Cases.		Jaundice.			Remission induced.		Outcome; comment. Condition after remission.
	Condition.	Duration, yrs.	Type.	Intensity.	Duration, wks.	Degree of relief.	Duration, yrs.	
Sidel, 1938.	3. Rheumatoid arthritis.	•	Catarrhal.	•	•	Marked relief of joint pains, "improvement dramatic."	•	•
	4. Rheumatoid arthritis.	•	Catarrhal.	•	•	Marked relief.	•	•
	Rheumatoid arthritis.	•	Unstated.	•	•	"Relief from pain."	•	•
	Rheumatoid arthritis.	40	Intrahepatic after vaccines.	Deep.	Few days.	Decrease in joint pains.	•	Two short attacks of jaundice within 3 weeks after two injections of autogenous polyvalent vaccine.
Durt, 1938	1. Osteo-arthritis.	•	Unstated.	•	•	Joints "cured."	•	•
Bauer, 1939	2 Arthritis stated.†	•	Jaundice after injections of gold.	•	•	Temporary cure.	•	•
	Chronic polyarthritis with psoriasis.	•	Clinchophen hepatitis.	•	•	Complete relief of joint pains.	•	Psoriasis unaffected during jaundice.
Ahlberg 1939	1 Secondary chronic polyarthritis	11	Intrahepatic.	Pronounced.	About 10.	Joint and muscle pains practically disappeared.	About 10 wks.	As jaundice faded, joint pains returned as before.
	2 Rheumatism (probably fibrositis).	15-20	Obstructive from carcinoma of pancreas	Marked.	•	"Entirely free" of rheumatic pains.	*Till death.	During jaundice rheumatic pains disappeared but abdominal (pancreatic) pains increased.
Lichtman, 1939	Rheumatoid arthritis.	10	Clinchophen hepatitis.	Icterus index, 27, S. B. R-t, 4.5 mgs.	About 6 wks.	Completely free of joint pains.	About 6 wks.	Joint pains returned.

* Data not stated or incomplete.
† S. B. R. means serum bilirubin.
‡ Durt's case 2 is listed as chronic infectious arthritis since gold was being given.

from stones, three of obstructive jaundice from pancreatic carcinoma, one case of obstructive jaundice from carcinoma of the ampulla of Vater, two cases of jaundice from fatal spontaneous subacute atrophy of the liver, one case of intrahepatic jaundice from neoarsphenamine and one from gold therapy, one of acute intrahepatic jaundice with chronic cirrhosis, two cases of jaundice of unstated type, and the following three cases of jaundice of unusual type. One patient received injections of an autogenous polyvalent vaccine to which he was sensitive; after each of two injections, given within three weeks, transient jaundice developed; having had rheumatoid arthritis for forty years which was unrelieved by many remedies, he was "very agreeably surprised" at the relief of symptoms which seemed to be initiated by the jaundice.³⁵ One case was labeled "emotional jaundice," apparently an acute intrahepatic jaundice which suddenly affected an arthritic patient one hour after he had seen his boy killed.⁶³ In a case of Thompson and Wyatt,⁷⁶ chills, repeated emesis, hemoglobinuria and marked destruction of erythrocytes developed after a transfusion of blood. The concentration of serum bilirubin rose to 12 mg. per 100 c.c., but jaundice persisted only five days. It may be questioned whether or not this was hemolytic jaundice. Because of its chemical difference from intrahepatic and obstructive jaundice it is important to determine whether hemolytic jaundice can induce the phenomenon.* In this type

* A form of hemolytic anemia occurs with lead poisoning; there is a marked destruction of circulating erythrocytes and an increased formation of erythrocytes by stimulated bone marrow. Jaundice occasionally occurs from destruction of erythrocytes and sometimes also from hepatitis. Pain in muscles and joints occurs not infrequently in lead poisoning.⁴ Hence it is of interest to note the following in Huxham's original description of the Devonshire lead colic published in 1738: "Sometimes a great many red itching Pustules, and often very burning and smarting, broke out with the Sweat all over the Body, which was of very happy Omen, as on this the rheumatic and colical Pains soon vanished.—This indeed was the most favourable issue of the Disease, but much more commonly the Rheumatism succeeded the Colic, the Colic the Rheumatism, and thus alternately tormented the miserable Patients, the Disease now being translated to the Limbs, now the Bowels. . . . The Appearance of a Jaundice sometimes took off the Colic for a time, but as soon as that went off the Colic immediately returned.—In one, or two Cases, however, a permanent Icterus absolutely carried off the Disease, some Pains only remaining in the Limbs."

jaundice is rarely marked; I saw one arthritic patient who was not relieved by mild hemolytic jaundice.^{27a} Minot noted a variable effect of pernicious (macrocytic) anemia on chronic infectious arthritis. The joints of one patient were distinctly better when she omitted liver extract and became so anemic that her skin was tinged yellow; the joints were notably worse when the anemia was under control. In other cases the reverse state of affairs occurred; joints and blood improved coincidentally.

"Gold jaundice" from hepatitis coincident with chrysotherapy may provoke the phenomenon according to some but not according to others. One of Burt's arthritic patients was taken ill with jaundice after injections of gold and temporary cure resulted. Hartfall, Garland and Goldie,²² however, noted no such effect. Jaundice, presumably of the catarrhal type, from toxic hepatitis, affected eighty-five of their 900 arthritic patients given chrysotherapy. The jaundice of twenty-two was slight, of fifty moderate and of thirteen severe (two died). Curiously no jaundice occurred in the first 100 cases. Later an epidemic of infective hepatic jaundice occurred in the region; perhaps some of their cases were of that type rather than gold jaundice. At any rate, the jaundice apparently had no ameliorating effect on the arthritis, not even in cases of severe jaundice. Indeed Hartfall, Garland and Goldie²³ later stated that results in those cases in which toxic jaundice developed were worse than in the others. Unfortunately, they reported no values for serum bilirubin. Because of this difference of opinion I shall quote a recent communication to me from an English physician³⁰ who was treating a patient with "acute rheumatoid arthritis" with gold salts. After three injections jaundice developed. "Within a week she had lost all the symptoms of rheumatoid arthritis, and now six weeks after the onset of the jaundice she is still absolutely free and doing the housework comfortably."

From all of the foregoing it is obvious that the type or quality of jaundice present is less important than its intensity or quantity.

SPECIFICITY OF THE PHENOMENON

Those who regard these various painful conditions which may be relieved by hepatitis and jaundice as entirely unrelated

diseases will consider the phenomenon nonspecific, but those who believe that chronic infectious (atrophic) and hypertrophic arthritis, fibrositis and perhaps even certain forms of sciatica are rather closely related rheumatic diseases will consider the phenomenon relatively specific. In support of the latter view were the observations that intercurrent jaundice of several types and varying severity did not alleviate the painful symptoms of nine of my patients with such conditions as gouty arthritis, toxic or infectious arthralgia, juxta-articular malignancy, ischemic neuritis and postherpetic neuralgia. Others^{33, 40} also noted no relief of pain in gouty arthritis during jaundice. With the onset of jaundice the patient of Ruiz-Moreno and Caruso with "rheumatoid arthritis" and old alcoholic polyneuritis⁶² noted disappearance of all articular pain and swelling, but no relief of the neuritic pain. No relief was experienced by two patients with brachial neuritis despite the presence of intense, prolonged jaundice.⁶³ During obstructive jaundice from pancreatic carcinoma Ahlberg's patient became free of rheumatic pain, but the abdominal (pancreatic) pain progressively increased.

ARE HEPATITIS AND JAUNDICE ANTIALLERGIC?

The following isolated observations suggest that the ameliorating effect of jaundice may operate rather widely. Dr. Hertzler, author of "The Horse and Buggy Doctor," for years suffered from recurring migraine which consisted of "intense attacks every two weeks with milder spells in between." Catarrhal jaundice with chills, fever and deep jaundice of unstated duration developed. In his book he wrote: "I can salvage one pleasant thought from this period: so long as the jaundice lasted I did not have a single attack of my weekly migraine." He was free of migraine for about five months; then it returned.*

Even more striking was the case of Boros: that of a man who had had intolerable ragweed hay fever, with severe asthma

*The effect of hepatitis and jaundice on migraine has since been investigated at The Mayo Clinic by Morlock and Alvarez. Among 215 patients with liver disease were sixteen who had had migraine; eight of them either lost their headaches or had fewer and milder ones after the appearance of jaundice or other symptoms of cirrhosis or biliary tract disease.

every August for eight or nine years. He took cinchophen for rheumatic pain of unstated duration. Thereafter, in August, 1935, when his hay fever had begun again, jaundice developed. Then "a momentous thing" occurred: a sudden complete cessation not only of the rheumatic symptoms, but also of the hay fever. A year later, in August, 1936, he still had no hay fever, asthma, or rheumatism and actually spent two weeks "where the ragweed literally abounded in countless numbers, enjoying his stay in complete happiness and comfort." Later, as a test, he inhaled ragweed pollen through the nose without any reaction, although skin sensitivity to injected pollen was still present.

In this connection a communication from a California physician¹⁶ is of interest: He encountered a case of well-established sensitivity to eggs, manifested by hives and gastrointestinal symptoms, in which obstructive jaundice developed from gallstones. During the jaundice and for some time thereafter the patient could eat eggs with impunity. Three months after the icterus index had become normal the sensitivity to eggs returned.

If these observations can be corroborated, it would appear that hepatitis with jaundice may invoke an antiallergic as well as an antirheumatic reaction. At any rate the phenomenon appears to be group specific rather than disease specific. This, of course, enhances rather than detracts from its possible therapeutic significance.

RELATED PHENOMENA

Effect of pregnancy.—Somewhat similar, though less dramatic, symptomatic remissions in chronic infectious arthritis can be induced by states other than jaundice; for example, on rare occasions by reactions to typhoid vaccine, not infrequently by almost any surgical operation, also by short periods of starvation, but especially by pregnancy. The last may initiate a physiologic state decidedly beneficial, at least temporarily, to patients with certain articular diseases. I recently reported²⁸ the effects of thirty-seven pregnancies on twenty-two patients: sixteen with infectious arthritis, two with psoriatic arthritis, two with periarticular fibrositis, one with intermittent hydrarthrosis and one with localized lumbar arthritis, presumably

infectious. Twenty of the twenty-two patients obtained marked, generally complete relief of articular symptoms during thirty-three of their thirty-four pregnancies and for variable periods thereafter. Others have described this phenomenon.⁷⁸ One arthritic woman obtained complete articular relief during each of nine pregnancies.⁵⁴ Incidentally, pregnancy often exerts a beneficial effect on psoriasis.^{84, 53}

Effect of cinchophen toxicity without jaundice.—Arthritic symptoms also may disappear in the presence of cinchophen toxicity without visible jaundice. One of my arthritic patients (case 16, first series²⁵) experienced complete relief of articular pain with the onset of cinchophen toxicity and urticaria, although jaundice did not appear until six weeks later. In nine of Rawls⁵⁷ cases of arthritis cinchophen toxicity and urticaria developed: in five cases (three of "rheumatoid" and two of "mixed arthritis") striking relief of symptoms was obtained. "There was reduction and in some cases disappearance of swelling, muscle spasm, fatigue, soreness and stiffness of joints with a marked increase in function." There was no visible jaundice. The icterus index varied between 5.9 and 12.5. Symptomatic relief lasted from three weeks to five months and was in general proportional to the severity and duration of the urticaria.

It seems probable that these phenomena, relief of articular pain by hepatitis with jaundice, by cinchophen toxicity and urticaria without jaundice, and by pregnancy, are closely related basically, if they are not identical. In normal pregnancy the liver is affected at least to the extent that tests of excretion of bilirubin reveal some retention.⁷²

ROLE OF THE LIVER IN THE PATHOGENESIS OF ARTHRITIS

Physicians have long suggested a relationship between hepatic dysfunction and certain articular diseases. According to French writers the basis of arthritism, the tendency to development of rheumatic diseases is "undoubtedly a hepatic deficiency."⁷⁷ In the past this conception was used in "an absurdly comprehensive way," and under the term "arthritism" were grouped together a host of presumably related conditions, including diseases of joints, psoriasis, migraine, urticaria and other exudative phenomena, hepatic disease, and so on. The

French also speak of a much less inclusive complex, "rhumatismes chroniques d'origine hépato-biliaire" or chronic biliary rheumatism, and Germans have described "arthritis posticterica." American and English^{1, 8, 11, 32, 33, 45, 61, 66, 77} writers often have referred to the supposed rôle of the liver in the production of arthritis. Jones considered intestinal and biliary infection the possible starting point of the chronic toxemia that causes chronic infectious arthritis. Normally the detoxifying function of the liver prevents intestinal infection from producing secondary changes in joints, but Rolleston⁶¹ suggested that bacteria may escape the hepatic filter by entering the circulation via the thoracic duct. According to others, arthritis results when the detoxifying function of the liver becomes impaired; if the liver fails to remove toxins from food and bacteria from the portal circulation, these toxins may irritate the joints; if the hepatic barrier were intact, arthritis of gastro-intestinal origin would not occur.

These ideas are vague, and currently most physicians do not incriminate the liver in articular diseases, simply because the few clinical, pathologic and laboratory studies which have been directed to the liver in arthritis have given little or no evidence of a relationship. But the idea persists. Some physicians regard the changes in serum proteins and the abnormal sugar tolerance curves, often present in chronic infectious arthritis, as evidence of dysfunction of the liver. Weiss recently considered articular stiffness, especially of hands and neck, one of the minor diagnostic signs of latent hepatic insufficiency. Sager also stressed a clinical relationship, for in 14 per cent of 208 cases of parenchymatous degeneration of the liver arthritis or severe arthralgia was present. Applying the Roche and Ehrlich tests, Watson noted dysfunction of the liver in from 50 to 70 per cent of cases of rheumatoid arthritis, osteo-arthritis and fibrositis. Rawls and his colleagues,^{58, 59} using various tests (excretion of azorubin-S, hippuric acid and bilirubin), noted evidence of dysfunction of the liver in about 50 to 60 per cent of 150 cases of chronic infectious arthritis. Hepatic dysfunction occurred in 25 per cent of the mild cases, 48 per cent of the moderately severe cases and in 73 per cent of the severe cases. These data are difficult to evaluate: hepatic dysfunction was not always pres-

ent, and when present was not consistent in type; the dysfunction was sometimes in the direction of a delayed excretion; at other times excretion was too rapid. Studies on hepatic function in cases of arthritis at The Mayo Clinic are similarly difficult to evaluate¹⁸ and what primary or secondary rôle, if any, the liver plays in the production or prevention of arthritis remains to be determined.

Nevertheless a liver, diseased in a certain way, is apparently advantageous to arthritic patients. Does this suggest that some sort of hyperhepatia or hyperfunctioning state of the liver was previously present, was related to the presence of the arthritis and was corrected by the hepatitis? Is something formed within the liver which has to do with a patient being rheumatic or allergic and is it possible that with a certain type or degree of hepatitis this agent is destroyed or no longer formed?^{10, 27*} Or do hepatitis and jaundice provide to tissues involved in arthritis and fibrositis some chemical substance, an adequate amount of which was not present previously? Is arthritis related to some hepatic hypofunction, some hypohepatia which the liver is stimulated to correct by the presence of hepatitis and jaundice?^{27*} Is some analgesic or antirheumatic substance produced by the liver in moderately effective amounts when the quantity of cinchophen used is too small to produce evident toxicity, but in excessive, dramatically effective amounts when cinchophen is used to the point of jaundice?^{33a} Lichtman³⁶ suggested that some endogenous toxic substance caused both the hepatitis and in his cases the sciatica, and that when the acute degeneration of the liver was severe enough to produce jaundice, associated disturbances in mineral and water metabolism occurred and contributed to the analgesia. Does the presence of hepatitis and jaundice influence the production of some potent immunologic agent? Are rheumatic patients relieved because more bile gets into their blood and reaches their joints and muscles, or because less bile gets into their intestines? Belding and Peacock have suggested that the important factor may be the absence of bile from the intestines "with all that this implies as to its cultural, chemical and solvent activities." However, many of the jaundiced patients experiencing the phenomenon had bile pigments in their stools and the phenomenon frequently lasted for weeks after the

color of the stools^{10, 25, 37} was normal. But this does not mean that the concentration of bile salts was normal in the bile reaching the stools. Space does not permit further discussion of these hypothetical considerations.

PRACTICAL SIGNIFICANCE OF THESE OBSERVATIONS

These observations lead to the inescapable conclusion that chronic infectious arthritis and fibrositis are not as inherently stubborn, uncontrollable and irreversible as the none too satisfactory results of current remedies would make us believe. If pregnancy, or hepatic injury with or without jaundice, rapidly can induce dramatic relief not only from pain, but also from swelling, stiffness and redness, obviously the body of the arthritic patient still possesses the capacity, if properly stimulated, to correct quickly and effectively the disturbed physiology underlying the symptoms of the disease. The problem is to try to find a proper and practical stimulus. If some potent common denominator of these corrective states, namely, hepatitis with or without jaundice, and pregnancy, could be uncovered and if the agent responsible for the relief and the mechanism whereby it operates could be discovered, a superior method of treatment, perhaps a rapid control, if not a cure, of these diseases would be at hand. Convinced of this idea, a number of workers have attempted by various means to reproduce the phenomenon in a practical, safe way.

EXPERIMENTAL THERAPY WITH HEPATIC, BILIARY AND RELATED SUBSTANCES

Human bile.—Fairly large amounts of human bile (as much as 2,600 c.c. in one day, 7,650 c.c. in ten days) were given^{27a} by stomach tube to a few arthritic patients.* No hyperbilirubinemia and no relief resulted. In view of the suggestion of Peacock and Belding that absence of bile in intestines might be advantageous to arthritics, it might be mentioned that the articular disease of patients, receiving bile orally, was at least not aggravated.

Natural bile salts.—Definite relief was not noted by my patients who received, orally, oxgall or glychotauro.^{27a} Sidel⁶⁷

* Hereafter in this paper arthritic patients will refer to those with chronic infectious (atrophic, rheumatoid) arthritis.

gave "ordinary bile salts" (bile salts, Fabry) orally to several arthritic patients; only one patient believed that he was benefited thereby.

Synthetic bile salts (decholin).—Several workers have used the synthetic bile salt, decholin sodium (Riedel de Haen), sodium dehydrocholate given orally or intravenously, in the main without results. Several of my arthritic patients received 2 gm. (10 c.c. of a 20 per cent solution) daily intravenously for from eight to twenty-one days, or tablets, 0.25 gm. each, orally in doses up to a total of 44.5 gm. in twenty-one days. Results were questionable. Sidel^{69, 70} also gave decholin intravenously to ten arthritic patients without noting consistently good results. One of the first patients^{69b} treated by this method seemed to be improved markedly after receiving injections of 10 c.c. of the 20 per cent solution daily for five days and less frequently thereafter. Relief was not noted, however, by other patients who received similar doses intravenously, sometimes daily for six days, sometimes once or twice a week for two or three months.^{69b} Little or no symptomatic improvement was noted by ten arthritic patients of Thompson and Wyatt⁷³ who received 2 gm. of decholin intravenously daily for nine to twelve days. Margolis also gave an unstated amount of decholin intravenously daily for a week to several arthritics without appreciable results. However, improvement seemed to occur in some cases in which Rawls⁵⁶ used 10 c.c. of a 20 per cent solution of the drug intravenously two or three times weekly for four to six weeks.

In contrast to these generally negative results have been those of Ruiz-Moreno and Tarnopolsky.^{64, 65} They gave 2 gm. of decholin intravenously daily for ten days to two patients with fibrositis of one and ten years' duration, respectively, and with symptoms referable to the liver such as dyspepsia after ingestion of certain foods, gas, belching, heart burn, occasional vomiting and pain in the right upper quadrant. During this treatment the hepatic symptoms were not relieved, but both patients noted complete relief of rheumatic symptoms for at least five months.⁶⁵ Subsequently a larger series of patients were treated similarly. Of the fourteen patients with fibrositis so treated, including one with sciatic fibrositis, eight (three of whom had hepatic dyspepsia) obtained complete relief; two,

marked relief, one, slight relief and three did not obtain any relief. Ten patients with rheumatoid arthritis were treated: relief of three, none of whom had hepatic symptoms, was great, and of two, slight. Five did not obtain relief. Three patients with osteo-arthritis were treated: one patient had complete relief of pain, one notable relief and one did not have any relief. The fibrositic element of the disease only was relieved. One patient with mild chronic rheumatic fever noted no relief.

When relief was obtained, it generally was noted during the first six injections. Focal reactions in joints, lasting ten to twelve hours, occurred after the first injection in four cases; when these occurred, subsequent injections gave no relief. The initial dose of decholin was 5 c.c. of the 20 per cent solution; if this was borne well, later doses of 10 c.c. each were given intravenously slowly, when the patient's stomach was empty. Of the twenty-eight patients so treated, nine (four with diarrhea) had generalized abdominal pain lasting one or two hours; one patient had a rather severe gastro-intestinal upset for twenty-four hours, which necessitated doses of 2.5 and 5 c.c.; doses later were increased to 10 c.c. No serious reactions occurred and it was never necessary to stop treatment. Later Tarnopolsky and Caruso reported the unexpected relief of pain in a case of cervicobrachial neuralgia due to cancer of the lungs when decholin was given intravenously; relief of pain persisted until death.

The experience of Ahlberg may help to explain why decholin presumably exerted an analgesic effect in some cases, but not in others. An elderly woman with an old painful chronic polyarthritis had spontaneous jaundice with almost complete disappearance of rheumatic symptoms. Articular pain returned while she still was slightly icteric. She was given 2 gm. of decholin intravenously and within an hour she was again practically free of pain for twenty-four hours. Later decholin was given intramuscularly for three days and the tablets were subsequently given orally without relief. After another intravenous dose notable analgesia recurred for twenty-four hours. One of Ahlberg's patients with sciatica obtained prompt relief about five hours after an intravenous dose of 2 gm. Other patients with muscular rheumatism, lumbago and sciatica noted no significant results. Ahlberg suggested that

the incompletely cured hepatitis may have been an important factor in the relief which followed the use of decholin. Perhaps decholin is ineffective unless a hepatic factor co-operates to produce analgesia. However, the presence or absence of hepatic symptoms did not seem to influence the results of Ruiz-Moreno and Tarnopolsky. Lichtman and Ahlberg suggested that the analgesia resulted from some hepatic influence on water balance. When decholin was introduced by Lichtman and Stern into the spinal canal of cats, no analgesic effect was noted.

Transfusions of jaundiced blood.—Four of my arthritic patients were given from one to four transfusions of highly jaundiced blood without significant relief to their joints.

Toluylenediamine jaundice.—One of my patients who had severe arthritis permitted me to give her toluylenediamine in an attempt to produce an effective jaundice. A marked but ineffective hemolytic jaundice was produced.

Liver extracts.—In my experience^{27a} and that of others the intramuscular use of certain commercial, antianemic, preparations of liver extract in ordinary amounts did not reproduce the phenomena characteristic of spontaneous jaundice. To two patients Margolis gave intravenous and intramuscular injections of autolyzed liver; articular pain, stiffness and soreness were increased, not decreased. Recently I have been giving injections of a special extract made from degenerated livers without striking results so far. Other physicians currently are investigating results of liver extracts of differing degrees of refinement.

Heparin.—Pelczar suggested that heparin might be partly responsible for the analgesic effect of hepatitis with jaundice. Heparin is presumably antiphlogistic. No results have been reported as yet.

Cysteine.—Shipton and Parr suggested that the effective factor in jaundice might be retention of cysteine, the reduction product of cystine in the blood, and that the beneficial effects of pregnancy may be due to an increased formation or retention of amino acids. Two patients with severe acute rheumatoid arthritis with pronounced skin atrophy presumably were relieved notably by daily intramuscular injections of 0.2

gm. of cysteine. Despite this, gold therapy was subsequently deemed necessary.

Cholesterol.—Cholesterol is said to be an important factor in the mechanism of immunity. The metabolism of cholesterol often is deranged in hepatitis and jaundice: the cholesterol in the blood rises in some cases but falls in most. The period of relief from arthritis during pregnancy roughly parallels the hypercholesterolemia of pregnancy. The proportion of cholesterol esters to total cholesterol generally, but not always, increased when symptoms of arthritis subsided during cinchophen hepatitis and urticaria without jaundice.⁶⁷ For these various reasons I have attempted to alter the blood fats of a few arthritic patients by various means, chiefly by the method of Corwin, and of Flock, Corwin and Bollman, so far without notable success. Results will be reported later.

Bilirubin.—Because the phenomenon described so often began when jaundice first became apparent, the dominant rôle could be ascribed to hyperbilirubinemia as was done by Najib-Farah.^{43, 44} According to this author bilirubinemia plays an important rôle in the processes of defense and immunity. Relief of pain, however, occurred in at least one of my cases (case 16²⁵) and in the first case of Sidel and Abrams some time before the appearance of visible jaundice, and in many cases it has lasted long after the hyperbilirubinemia has disappeared. Although the rheumatic symptoms in Boros' case suddenly stopped with the onset of jaundice the symptoms of hay fever disappeared just preceding the onset of jaundice. Rawls¹⁵⁷ patients obtained articular relief during cinchophen toxicity without visible jaundice. For these and other reasons, and despite the fact that the serum content of bilirubin is slightly subnormal among arthritic patients,^{53, 75} I have not believed that bilirubin was the analgesic agent or that relief could be obtained by injections of bilirubin, at least of the indirect-reacting bilirubin preparations commercially available. In spontaneous jaundice relief generally was not noted until the serum bilirubin gave a direct van den Bergh reaction.

Injections of solutions containing 10 to 15 mg. of bilirubin per kilogram of body weight were given daily by Thompson and Wyatt⁷⁶ to three patients with chronic infectious arthritis. Slight hyperbilirubinemia and icterus resulted with little or no

symptomatic relief. Smaller doses of 3 mg. or less per kilogram of body weight were given by Rawls⁵⁶ to several patients without relief.

Bilirubin and decholin.—Although injections of bilirubin or of decholin separately had produced no amelioration, Thompson and Wyatt^{75, 76} noted that repeated daily injections of solutions containing 10 to 15 mg. of bilirubin and 40 mg. of decholin per kilogram of body weight produced a beneficial effect "which apparently duplicated the effects" of spontaneous jaundice. The mixture of bilirubin and decholin produced a slightly higher and more persistent hyperbilirubinemia than injections of bilirubin alone. From six to twelve injections were given to sixteen patients with chronic infectious arthritis. Icterus and notable hyperbilirubinemia were produced, which lasted from fourteen to twenty-three days. Concentrations of serum bilirubin finally reached peaks about 15 mg. per 100 c.c. twenty-four hours after a previous injection. Van den Bergh reactions were at first indirect, later direct. Symptomatic remissions were induced in fourteen of the sixteen cases. In eight cases the remissions were short, lasting from five to forty days; in six cases the remission were long lasting from two to thirteen months. Diminished swelling and pain characterized the remissions, some of which were complete; others were incomplete. Thereafter symptoms returned, sometimes to the same degree as before but generally in milder form.

By this method, with variations which we considered minor, Mackenzie, Kendall, Lundy and I²⁹ treated twelve patients, eleven with chronic infectious arthritis, one with fibrositis.* Rarely noting any significant effect from six to twelve injections we often gave twelve to twenty, sometimes twenty-five to thirty, consecutive daily injections. Deep icterus and hyperbilirubinemia were induced; concentrations of serum bilirubin were frequently much higher than those obtained by Thompson and Wyatt. One patient had a rather complete symptomatic remission, but only for about three weeks—which was the longest, most definite effect obtained. Six patients experienced short, incomplete remissions for a few days only. Five patients noted little or no relief. In our

* We are greatly indebted to Dr. David Klein and the Wilson Company, Chicago, for the bilirubin used in these experiments.

hands this type of artificial jaundice gave meager and inconsistent results which at best were very inferior to the effects of spontaneous jaundice. We are inclined to believe that such improvement as Thompson and Wyatt and we obtained did not result directly from the substances injected but indirectly from their effect on the patient's own liver. Van den Bergh reactions on the commercial bilirubin before injection and on the serum after the first doses were indirect; after several doses reactions on serum became direct. Is it likely that the occasional relief came, not from the artificial or exogenous jaundice, but from an endogenous jaundice and hepatitis which the injections finally fostered? Because of the expense of bilirubin, the frequency of annoying venous thrombosis from the injections, and the results we obtained, I cannot agree that this method is practical or represents an adequate "control of arthritis."⁸³ But the fact that any relief at all can be induced in such a novel way makes this method worthy of further study.

CONCLUSIONS

The observations summarized herein indicate that hepatic damage, generally with, but occasionally without jaundice, may initiate physiologic reactions which are decidedly beneficial to patients with certain conditions, especially certain rheumatic diseases. They indicate that the future outlook for patients with chronic infectious arthritis is decidedly hopeful and that, within the body of patients who have even the severest arthritis, powerful corrective forces lie dormant which merely await the proper stimulation. Somehow or other pregnancy and certain forms of hepatitis with or without jaundice may provide the proper stimulus, following which a rapid and dramatic, even if temporary, recovery from arthritis may occur. A continued search should be made for some practical and safe way to induce similar remissions at will. I regard the efforts so far made by myself and others as relatively ineffective and falling far short of what may be accomplished eventually. I believe that the therapeutic methods considered herein should be regarded as laudable research ventures not applicable to general practice. But I believe, or at least hope, that perhaps we are working in the right direction even if we have not yet found the right road.

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ALLERGY TO FOODS IN ADULTS, WITH A NOTE ON THE PROPHYLACTIC USE OF HISTAMINASE

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Although the frequency with which food allergy occurs is greatest in childhood, and becomes less and less as age increases, there are many adults who are food-sensitive and, contrary to what might be expected, the difficulties of diagnosis of food allergy actually increase in the adult group. There are several reasons why food allergy presents such a difficult diagnostic problem in adult life: One reason, not often mentioned is that, as persons become older, the incidence of organic gastro-intestinal conditions increases and, also accompanying increased age, are responsibilities and nervous strains which increase markedly the functional causes of symptoms. It thus becomes necessary, particularly for adults, to differentiate between an *allergic sensitivity* to a specific food or foods and an *intolerance* to a food or foods which has its cause not in allergy, but in some organic or functional disturbance. The qualitative dyspepsia as exemplified by intolerance to fats, cooked cabbage, onions, raw apples, radishes, cucumbers and other foods, experienced so commonly by patients who have cholecystic disease with or without stones, or who have peptic ulcers, is generally recognized, yet not infrequently this type of dyspepsia or intolerance to food is confused with food allergy. The intolerance to certain foods that is experienced by patients who have chronic gastritis arising from various causes, or by occasional patients who have achlorhydria or atrophic gastritis, also may be confused with food allergy, particularly if the patient's examination is limited to an allergic investigation. The gas and epigastric distress experienced soon after eating by many patients who have diaphragmatic hernia may also raise the question of food allergy. These are only a few of many organic conditions that could be cited that produce symptoms of food intolerance which could be mistaken for food allergy.

Even more important and frequently more difficult of diagnosis is the host of *functional* conditions in which the patients have food intolerance as the important presenting complaint. Persons who are nervously exhausted, and others who are excessively stimulated, such as, for instance, those who have migraine and pylorospasm, or those who eat too rapidly and too much, or those who are inclined to hyperacidity and to smoke and drink excessively, are frequently heard to relate their intolerance for certain foods.

The frequency with which food intolerance of various types is encountered can be easily demonstrated if the conversation at lunch or dinner is turned to one's own idiosyncrasies concerning food, which in turn probably will encourage others at the table to call attention to their intolerance to certain foods. This type of survey, however, gives no indication of what part food allergy actually plays in these intolerances, even if it is brought out by questioning that some or all of the individuals are allergic. It should always be remembered that allergic individuals are subject to functional and organic diseases, just as are nonallergic individuals. To obtain any real information about the intolerance to foods of friends at the dinner table, it would be necessary in each instance to carry out a careful general examination supplemented at least by such gastrointestinal and allergic or other investigations as the symptoms, in each case, would warrant. Only in this way would it be possible to determine which intolerance to food was the result of specific food allergy, which was the result of organic disease and which was the result of functional causes.

It must not be assumed, from the foregoing, that intolerance to food or food allergy evidences itself only in the gastrointestinal tract. True food allergy may produce a host of different reactions or symptoms in different ways and in different organs in different individuals. For example, several individuals may be sensitive allergically to chocolate, so that in one individual aphthous ulcers may follow its ingestion; in another, severe migraine results; in still another, nausea, vomiting, abdominal cramps and diarrhea may ensue and in yet another acute severe urticaria and angioneurotic edema may develop.

Diagnosis.—The first point to be emphasized, therefore,

is the necessity for a proper approach to the question of sensitivity to foods, and this, we feel, should be provided by means of a careful *history* and an inclusive *general examination*, supplemented by whatever *special examinations*, such as gastrointestinal studies, roentgenologic, rhinologic, dermatologic, neurologic, allergic or other investigations, as the patient's symptoms may require. It might be stated that a diagnosis of food allergy arrived at by *excluding* all other causes is more likely to be sound than a similar diagnosis arrived at by means of any allergic tests now in use.

One of the most disappointing diagnostic methods in medicine today is that of *cutaneous testing with food antigens*. Regardless of the technic used, a large number of false positive reactions to tests are constantly being encountered, and also, rather frequently, negative reactions to tests are encountered in cases in which the patient's symptoms would indicate that true food allergy exists. Although this fact seems to be generally recognized, it does not explain why such large numbers of cutaneous tests with food antigens continue in such common use. For all the information food tests give the physician and patient, most of such testing might well be discontinued entirely. Recognizing the inadequacy of cutaneous testing with foods, various other diagnostic methods of testing for sensitivity to foods have been tried, but without encouraging results to date. This failure to provide accurate methods for the demonstration of specific sensitivity to foods has made it necessary to resort to various trial methods of diet, sometimes referred to as "elimination" or "exclusion" diets. The principle of such dieting rests on the observation of the patient and physician that when the patient eats a certain food in sufficient quantity, a certain train of abnormal symptoms results, whereas if that food is entirely excluded from the diet of the patient, the symptoms will not occur. From the practical as well as the scientific standpoint, it is necessary to repeat experimental observations several times to avoid the diagnostic pitfall so commonly encountered in medicine of *post hoc, propter hoc* reasoning. The observation, for instance, that urticaria developed as a result of a patient's eating nuts cooked in cottonseed oil is pointless unless it is confirmed by further experiments with the different foods concerned.

TREATMENT

Elimination diets.—Sensitization to a single food may occur, but it is more common to find the adult allergic to *several* foods. These foods may be botanically related, or on the other hand, as far as can be determined, may be entirely unrelated. In formulating an elimination diet for an adult, several methods may be followed. No matter what method of elimination diet is used, it is sufficiently clear without explanation to say that if the physician has the co-operation of a dietitian who understands the principles of food allergy, as well as the principles of nutrition, the problem for both the physician and the patient will be greatly simplified. Another great help is to be able to have the patient eat under controlled conditions, such as at a hospital or at an outpatient diet kitchen when the latter is available.

There is no consensus as to what type of elimination diet should be used in searching for offending allergic foods. It is entirely an individual problem; the physician is searching for an unknown offending food or foods and there are many ways of conducting the search. Each physician who has had, of necessity, to carry out such an investigation on a number of occasions has developed his own approach to the problem of eliminating certain foods and substituting others, until the gamut of clinically important foods has been run and the necessary observations have been made. Provided that the survey is carefully and completely done, who can say that one series of diets is superior to another? It should be emphasized and re-emphasized, however, that any elimination diet is a *trial diet* arranged for the sole purpose of learning what foods are tolerated and what foods are not tolerated by the patient. Once those foods which are not tolerated are known, they are entirely avoided and suitable substitutes which are usually readily found are included in the diet. A supposedly adequate diet, excluding the offending articles, is thereafter eaten by the patient. Since multiple sensitivity to foods is the rule, the practical solution is not easy, and the final diet which excludes all known offending foods must be scrutinized most carefully for the reason that the final diet is the one on which the patient must live and work. Semi-invalidism must not result because of the patient's diet. For purposes of testing during a period

of a few weeks, a basic elimination diet is probably safe, but for longer periods such an elimination diet is nearly always a deficient diet. Too often does the physician encounter patients whose diet, based on cutaneous tests with foods, or elimination diets or other methods of testing for food allergy, is obviously inadequate in one or many features. Adequate consideration had not been given to the protein, mineral, bulk, vitamin, iron or caloric requirements of the patient.

For example, the following menu from a patient's elimination diet shows the day's diet to be low in calcium, phosphorus, vitamin B, and probably iron. Unless large servings are eaten, the diet may be low in fat and protein content. Milk and eggs are not included in the diet, and therefore are not used in cooking.

<i>Breakfast.</i>	<i>Dinner.</i>	<i>Supper.</i>
Peaches	Roast lamb	Cold chicken
Rice	Peas	Asparagus tips
Karo corn syrup	Corn pone	Rice biscuits
Rice biscuits	Lettuce salad with lemon juice and	Olive oil
Olive oil	olive oil	Pineapple tapioca
	Canned pears	

Fortunately for allergic children, most pediatricians recognize the aforementioned facts, but the allergic adult occasionally does not fare so well, long-standing elimination of certain needed foods having resulted in scurvy, pellagra, and other less marked deficiency states. It is important, therefore, to keep under observation the patient who is sensitive to foods, not only so that he can be assisted with his eliminations of food from his diet, but equally important, so that it can be ensured that his diet over a period will be nutritionally adequate. In this instance, again, the assistance of a graduate dietitian is invaluable to the patient and physician. Under the present economic system in the northern half of our country which attempts to provide an "adequate diet" for each individual, it may be conjectured whether the dietary deficiencies that occur are not more often due to poor advice than to the economic status of the individual.

One simple method of arriving at a correct elimination diet is to observe the patient for several days while he is eating a diet restricted to only a few foods which are known rarely to cause allergic or other reactions, some such foods, for example,

as corn, rye, soy bean flour, tapioca, corn oil, olive oil, gelatin, lamb, carrots, lettuce, asparagus, beets, pears, peaches, apricots, plums, sugar and tea. For illustration, it may be assumed that a patient is experiencing frequent severe headaches which are suspected to be caused by food allergy, and it may also be assumed that he has no headaches when he is eating rice, pears, tea, butter, lamb, gelatin and tapioca. With the gradual addition of new foods to the diet it is determined and later confirmed that the addition to the diet of chocolate and milk resulted in headache. It would, then, be a comparatively simple matter to arrange an entirely adequate diet which did not contain these offending foods. The physician should then study further the possibilities that the patient could tolerate milk substitutes or powdered or condensed milk. If it is necessary to eliminate milk entirely from the diet, it would be well to add calcium gluconate or lactate to the diet. Dicalcium phosphate, also, should be added to the diet deficient in milk to overcome a possible deficiency in phosphorus. Should it become necessary to eliminate other foods, such as citrous fruits, from a diet, the vitamin C content of the diet would be reduced thereby, but this lack can be replaced by using cevitic acid tablets. A deficiency of the vitamin B complex may occur in diets in which whole grains must be eliminated, and this deficiency also will require appropriate supplements. Vitamin A is found in a number of different foods, and a deficiency of this vitamin is not likely to occur unless many foods have been eliminated from the diet. Should the diet be deficient in vitamin A, however, carotene could be added to the diet. Finally, the diet should be scrutinized for its content of iron, particularly in the case of female patients.

It should be explained at this point that elimination diets are of practical value only if the allergic symptoms of the patients occur at frequent intervals—at least once a week. When allergic symptoms occur at greater intervals than this, some form of an allergy diary is better fitted to reveal the desired information. When allergic symptoms occur at long intervals, and if they are referable to food, the symptoms will probably be found to be caused by a food which is rarely or infrequently eaten, and not by everyday articles of diet. A record of unusual foods eaten within twelve hours of the allergic reaction

should prove of diagnostic value. Having determined that a specific food is the probable cause of the allergic reaction it is essential for the physician to prove that this food will always cause the syndrome.

The usual method of carrying out an elimination diet is to follow Rowe's elimination diets or some modification thereof. In such a course the physician has a choice of four or five groups of foods, each group being different from any of the others, yet each containing essentially some type of meat, a small group of vegetables and a few fruits, a beverage, fat or oil and a cereal. Starting with any one of the diet groups, the patient is observed for a test that usually need not exceed a period of ten days. Should no relief of the patient's symptoms occur, this first trial diet is discontinued, and a totally different group of foods is tried. This procedure is repeated until a group of foods is found which does not cause the patient to manifest the allergic symptoms under consideration. This diet, then, represents the basic diet to which the patient now gradually and cautiously adds a new food or foods at about three or four day intervals. Should any allergic reaction occur, the most recently added foods are eliminated. In practice, this is not as simple as it sounds, for it requires patience and intelligence and a thorough understanding by the patient of what is being attempted. Complete co-operation is essential. In defense of the patient, however, let it be said that his or her failure to obtain relief while undergoing this tedious process is just as likely to indicate that something other than allergy to food is responsible for or contributing to the symptoms complained of, as it is to indicate that the patient did not follow instructions. As a result of the recent publication of a manual and recipe book for those who suffer from allergy to food, many of the problems of arranging a palatable and yet adequate elimination diet are materially lessened. This book, by Helen Morgan, is entitled *You can't eat that*, and is not only a storehouse of recipes that do not contain this or that ingredient, but it includes information concerning what foods, condiments, flavors, and the like are used in a very extensive list of trademarked or proprietary foods, together with other useful information, both general and specific, about allergy to food.

One of the more discouraging features of the so-called

elimination dieting is that careful studies may reveal well-confirmed sensitivity to one or several foods, and yet in spite of avoiding these foods the patient's symptoms continue. To eat the offending foods would promptly result in a flare-up of symptoms, true enough, but avoidance of such foods had not entirely or satisfactorily relieved the patient. Some food or some product of digestion capable of producing noxious symptoms apparently had been overlooked.

Histaminase.—Into this rather gloomy picture of allergy to food has finally come a ray of hope in the form of a tissue extract having certain detoxifying powers on histamine. It has long been conjectured that the H-substance of Lewis, more recently shown by Code^{2, 3} to be histamine, plays an important rôle in allergic and anaphylactic reactions. Although liberation or production of histamine may be only one phase in the complex chemical process of allergy, if the physician was able to control or neutralize this one phase, the result might well interrupt the cycle that results in distress to the patient. It has been shown by Dr. Roth at The Mayo Clinic, that certain physiologic effects that follow injections of histamine can be prevented or neutralized if this tissue extract, which was first designated by Best and McHenry as "histaminase" because of the enzyme-like properties against histamine which it possesses, is first administered orally or parenterally.

Just what happens when an allergic patient eats a food to which he is allergically sensitive is not known. It has been shown by Code⁴ that anaphylactic reactions are accompanied by a sudden transient liberation of histamine and it is now generally thought that histamine is involved in the production of the allergic reaction. Additional support of this assumption is given by the almost uniform clinical observation that ingested histaminase will permit patients to eat foods to which they are otherwise allergically sensitive. Taken twenty' to thirty minutes before eating, several enteric-coated tablets of histaminase will permit most patients allergically sensitive to foods to eat the offending foods, unless the hypersensitivity is an extreme one. When sensitiveness to food is very marked, it is still good policy for the patient to avoid the offending food, but the prophylactic use of histaminase has definitely controlled most minor and moderate reactions to food, and has permitted the

patient to eat an adequate diet. As physicians become more experienced in dosage, perhaps all allergic reactions to food can be obliterated but thus far this has not been accomplished. The effect of histaminase as it is now used at The Mayo Clinic is a transient one and it apparently has no effect on the inherent allergic status of the patient, inasmuch as the patient's symptoms seem to return when the administration of histaminase is stopped. The effect of histaminase on allergy to food is apparently satisfactory whether the reacting tissues are in the skin, the respiratory tract, gastro-intestinal tract, or other regions.

A great amount of study must yet be done and more clinical experience obtained with this tissue extract before it can be stated exactly just how useful or how limited will be the value of the extract in the treatment of allergic conditions, but as has been stated, it seems at the present time to offer the greatest promise of help in this difficult problem of allergy to foods.

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CUTANEOUS MANIFESTATIONS OF DISEASES OF LIPOID METABOLISM

HAMILTON MONTGOMERY

Recognition of the various cutaneous manifestations of diseases of lipid metabolism and especially various types of cutaneous xanthomatosis is of importance to the physician not only from the standpoint of diagnosis but also in regard to prognosis and treatment.^{13, 15} Frequently, cutaneous lesions may be the first sign of serious systemic disease of various types.¹²⁻¹⁵ Concepts regarding the group of lipid diseases in general have undergone many modifications in recent years as the knowledge of the physicochemistry and of the metabolism of the lipoids has gradually increased. Various classifications of diseases of lipid metabolism have been given^{13, 15} including recent ones by Thannhauser and Magendantz and by Held. The latter would divide lipoidosis into (1) malignant disease and (2) benign (primary) disease; yet, in my experience, many conditions in this second group frequently offer a serious and often fatal prognosis.

The following presentation and classification are given from a dermatologic viewpoint but the systemic manifestations are emphasized. It can only be regarded as a tentative classification in view of our present inadequate knowledge of lipid metabolism. It is impossible to give complete references to controversial points which are adequately covered in the recent articles cited and the bibliographies appended thereto.

LIPOID PHYSIOLOGY

An understanding of the physicochemistry of lipid metabolism is fundamentally important. Newer concepts in this field have been reviewed in part by Held in the *Medical Clinics of North America* of August, 1939; also by Cantarow and Trumper, Parsons, Sperry, Wiggers and Wilder. The terms "lipids" and "lipoids" have been used loosely and interchange-

ably in the literature. Strictly speaking, the lipids include (1) the ordinary fats, (2) the lipoids including phosphatides, fatty acids and cerebrosides and (3) the sterols including cholesterol, dihydrocholesterol, coprosterol and so forth. We are not concerned here with the physiologic mechanism of chemical separation of lipoids from the intestinal tract. It is known that the sterols including cholesterol are synthesized in the body but the mechanism and the site of the synthesis remain unknown. Cholesterol and cholesterol esters are present in every lipid mixture. Cholesterol is a hydrophobic colloid and plays a part not only in the exchange of fat-soluble material but also in the exchange of fluid. Herbivorous animals cannot excrete cholesterol, which explains the ease with which hypercholesterolemia and subsequent atheromatosis are obtained in such animals by feeding cholesterol. The phytosterols of plants are not abstracted by either herbivorous or carnivorous animals. Hence, the value of a diet free of animal fat in the treatment of certain types of xanthomatosis.

Normally, there is a comparatively consistent ratio between free cholesterol and cholesterol esters (combined cholesterol) which ratio may be disturbed in certain types of lipid diseases.^{18, 22} The phospholipids probably are formed in the liver, carry oxygen to the cells and play an important rôle in the physiologic function of the cells.^{3, 20, 24} Some authors believe that there is an antagonistic physicochemical reaction between cholesterol and the phospholipids. It would appear that different organs in the body play primary and secondary rôles in various types of diseases of lipid metabolism. Especially to be mentioned are the liver, pancreas, pituitary gland, spleen, adrenal glands and even the thyroid gland and the sex organs.^{3, 17, 20, 24} There is a close relationship between vitamin A and carotin. Vitamin D has recently been thought to be derived from cholesterol and not from ergosterol.²⁴ There is a close relationship between vitamin D and various hormones. Disturbances in the metabolism of vitamin C, of vitamin B complex in relation to hepatic disease and disturbances of lipid metabolism may also be factors in increased pigmentation of the skin. The lipochromes are composed of cholesterol-like chemical substances.

It is fundamentally important to make a chemical analysis

of blood plasma and tissue lipoids, not only of cholesterol but of all the other lipoids. Comparison of divergent points of view in regard to diseases of lipoid metabolism has been difficult because of lack of uniformity of methods of chemical analysis employed including unreliability of the older methods, frequently failure to make any determinations except in regard to cholesterol and often failure to establish normal values by analysis of a sufficiently large group of cases.

It is important to recognize that the newest methods of blood lipoid determinations vary considerably in regard to normal figures according to different methods of analysis used. The following are mean normal values for lipoids in milligrams per 100 c.c. of plasma according to methods of analysis by Bloor and for lecithin by Whitehouse: total cholesterol, 200; cholesterol esters, 145; lecithin, 250; total fatty acids, 350, and total lipoids, 550. The mean value for lecithin by newer methods of analysis by Youngberg and Youngberg is about 225.^{1, 14} Total cholesterol plus total fatty acids equals total lipoids. Lecithin represents phosphatide-P times twenty-five. Thannhauser and Magendantz have emphasized that in Niemann-Pick disease the diamino phosphatides (sphingomyelin) rather than the mono-amino phosphatides which include lecithin and cephalin play the important rôle. One must remember that there is a marked fluctuation from the mean normal value and that there is a marked fluctuation according to the age of the patient, being highest between the ages of fifty to fifty-nine years according to Barker when the mean normal values for the blood in milligrams per 100 c.c. were: cholesterol, 244; cholesterol esters, 174; phospholipids, 235; fatty acids, 384, and total lipoids, 628. Blood lipoids are usually low at birth and the mean figure for cholesterol, for instance, in the second decade of life in Barker's series was only 160 mg. per 100 c.c. of plasma. Determination of blood plasma lipoids should always be made when the patient is in a fasting state.

Determinations of lipoids in blood plasma or tissue reveal surprisingly little variations when repeated daily analyses are made. There may, however, be marked variations associated with diet in regard to the lipoids of blood plasma. An increased intake in phosphatides or a fasting diet may result in hyperlipemia and hypercholesterolemia, whereas increase in

the content of cholesterol in the diet, at least experimentally in dogs, has no effect.²

There may be cyclic alterations in blood lipoids in women especially in relation to the menstrual cycle, a fall in cholesterol occurring during the menstrual period but preceded or followed by a hypercholesterolemia. Hypercholesterolemia and mild to moderate hyperlipemia are also seen in association with pregnancy and also with obesity and in men who have a pyknic rather than leptosomatic type of build.

The total lipoids of normal skin from which the subcutaneous fat has been carefully trimmed form less than 3 per cent of the wet weight of the tissue which has been subjected to immediate analysis; 5 to 15 per cent of the total lipoids are in the form of cholesterol, and lecithin varies from a trace to 30 per cent of the lipoids. Further determinations of histochemical content of normal skin from various regions of the body should be made especially as recent studies indicate variation in lipoid content in different areas in experimental animals.²¹ Differences in comparative figures regarding the proportion of the various lipoids on the basis of immediate analysis of the wet weight and proper methods of dry chemical analysis should be of insignificant degree.

SYSTEMIC DISEASE ASSOCIATED WITH HYPERLIPEMIA

There are many diseases in which hyperlipemia and usually hypercholesterolemia is a more or less constant finding. Hypercholesterolemia is almost a constant and diagnostic finding in myxedema. Hyperlipemia is of frequent occurrence in various types of nephrosis including so-called lipoid nephrosis. More will be said later regarding hyperlipemia in regard to coronary sclerosis, angina pectoris and occlusive vascular disease of the extremities. There is an increase in lipoids, more often of free cholesterol, in cases of obstructive jaundice with or without cutaneous xanthoma. Hypercholesterolemia and hyperlipemia have frequently been reported in cases of diabetes mellitus. Recent studies show that the increase is usually slight and inconstant except in cases of diabetic acidosis.⁹ Fatty acids are increased more than the cholesterol. There is earlier development of arteriosclerosis in cases of diabetes and a higher incidence of arteriosclerosis among women who have diabetes

than in cases of arteriosclerosis without diabetes.¹⁹ This, however, remains a debated point; whether a high-fat diet has anything to do with the development of the arteriosclerosis in cases of diabetes²⁵ is also subject to differences of opinion. Frequently reported is an increase in cholesterol associated with allergic conditions, including asthma and hay fever. A rare form of febrile cholesteatoma has been described by Edelman. Hyperlipemia and hypercholesterolemia are also seen in emaciated individuals who have undergone forced starvation⁷ and frequently are also associated with terminal states of systemic disease in relation to deficiencies of vitamin A or B and in association with chronic hemorrhage. Variable changes in cholesterol and phosphatides occur in the tissues and in the blood in various types of cancer.

SYSTEMIC DISEASE ASSOCIATED WITH HYPOLIPEMIA

Hypolipemia, and usually hypocholesterolemia as well, is a valuable diagnostic sign in myelogenous leukemia and also in some cases of hypochromic anemia. It is also seen, but not constantly, in hyperthyroidism, primary hepatic cirrhosis and acute atrophy of the liver and at the climax and terminal stages of febrile infectious diseases, probably the result of the action of cholesterol on bacterial toxins; also it is encountered in some cases of epilepsy and in some cases of rheumatic heart disease.

CUTANEOUS DISEASES SECONDARILY ASSOCIATED WITH DISTURBANCE OF LIPOID METABOLISM

Cutaneous diseases associated secondarily with disturbances of lipid metabolism include psoriasis, eczema, leprosy and syphilis. Hypercholesterolemia occurs in many but not in the majority of cases of psoriasis and is not a constant finding. Some authors have claimed good results from low-fat diets or from diets free of animal fat but this has not worked out in our experience at The Mayo Clinic in most cases of psoriasis. The use of the cholesterol tolerance test advocated by Bürger and Grütz seems to be of doubtful value. Infantile eczema especially has been attributed to an insufficiency of fatty acids and lowering of the iodine number of the fatty acids of the serum. Beneficial results reported from the use of

linolenic acid and so forth have not been substantiated by the more recent studies.¹² It is important, however, to emphasize here the rôle played by unsaturated fatty acids in regard to nutrition in general. Recent studies by Hopkins and others show some hyperlipemia and disturbance of lipoids in leprosy especially in cases in which xanthelasma of the eyelids also was present. Rosen has emphasized that a moderate increase of cholesterol occurs in various stages of syphilis.

CUTANEOUS LIPOIDOSIS WITHOUT EXTENSIVE SYSTEMIC DISEASE

There are a few diseases of lipid metabolism limited essentially to the skin.

Sclerema neonatorum.—Gray described two types of sclerema neonatorum; the first is characterized by localized regions of solidification of fat occurring about the cheeks, shoulders, arms and legs in otherwise normal children shortly after birth. The waxy appearance of the skin is apparently due to deposition of crystals of palmitin and reduction of the amount of olein present in the subcutaneous fat that results in a rise of the melting point of the fat. McIntosh and others, however, would regard this type of sclerema neonatorum as akin to *subcutaneous fat necrosis of the newborn infant* in which bluish-red indurated lesions appear at birth or shortly afterward, probably the result of obstetrical trauma. Gray's second type of sclerema neonatorum involved weak, premature, marasmic infants who, at any time before six months of age, experienced the development of diffuse solidification of the fat of the entire body, usually with fatal termination. This type has been designated by some as a preagonic induration.

Lipoma.—Solitary or multiple lipomas usually develop in adult life. The cause is unknown. They are essentially benign lesions.

Adiposis dolorosa (Dercum's disease).—Adiposis dolorosa is characterized by irregular subcutaneous fatty masses associated with pain, presumably due to pressure on cutaneous nerves.

XANTHOMATOSIS

The following working classification which differs in some respects from that given by Thannhauser and Magendantz and by Held is presented, emphasis being placed on the cutaneous

manifestations and distinction of types because of difference in type of lipoid disturbance and differences in regard to prognosis and treatment.

So-called systemic types or those primarily of systemic origin.*—*Hand-Schüller-Christian disease.*—This syndrome is usually seen in children but sometimes appears in adults. It is characterized by rarefaction of the bones of the skull, occasionally of other membranous bones, diabetes insipidus, exophthalmos, various abnormalities in growth including adiposogenital dystrophy and also gingivitis and stomatitis. Frequently, cutaneous xanthomas of different types are present, especially the disseminate type. The disease may begin with involvement of the middle ear and the typical triad of the first three symptoms mentioned are frequently lacking. There is an increase in cholesterol in the tissues involved which show the characteristic histologic picture of ordinary xanthoma. There may or may not be hyperlipemia and hypercholesterolemia. Roentgen therapy results in partial to complete involution of the rarefied portions of the bones. The disease is usually fatal when it develops in children. It may even involute spontaneously when it develops in the later decades of life.

Niemann-Pick disease.—This disease begins in infants of Jewish extraction. It is characterized by splenohepatomegaly although any organ or bone may be involved in the typical xanthomatous process. There is a peculiar yellowish hue to the entire skin without any deposition of lipoids in the skin. Cutaneous xanthomas are a very infrequent finding. Chemically, as Thannhauser and Magendantz pointed out, there is a disturbance in phosphatide metabolism especially in the diaminophosphatides (sphingomyelin). Tay-Sachs disease or amaurotic familial idiocy is probably a variant of Niemann-Pick disease in which there is a mental retardation associated with deposits of lipoids in the brain. Niemann-Pick disease is rapidly progressive and fatal.

Gaucher's disease.—This syndrome may occur at any age and tends to be familial and most frequent in members of the Jewish race. The spleen is chiefly involved (marked enlargement) but the liver may also be involved. There is a mottling

* For a more complete description, see Held.

and rarefaction together with cortical thickening of the long bones and frequently cuneiform thickening of the conjunctiva near the cornea; these changes are of diagnostic value. There is a peculiar bronze color to the skin. There may be hemorrhagic tendencies. No typical cases have been described in association with cutaneous xanthoma. Histochemical analysis reveals typical large xanthoma or foam cells with deposition of cerebroside, especially kersin in the regions involved. The course of the disease is chronic and exhausting. Death may result from intercurrent infection. Splenectomy has been advocated as a method of treatment.

Cutaneous types of xanthomatosis.—There are many distinct cutaneous types of xanthomatosis although occasionally the merging together of two or more types may be seen in the same individual. This is especially true in children. Carotinemia and xanthochromia may also occur in association with practically any type of cutaneous xanthoma or may occur entirely independent of any disturbance in lipid metabolism.

Nevoxantho-endothelioma (McDonough).—This type is characterized by the development in the first few weeks of life of a group or groups of yellowish to yellow-brown papules or nodules occurring chiefly on the extensor surfaces. The blood lipoids are normal. There is a characteristic histologic picture of endothelial giant cells as well as deposition of lipoids in typical xanthoma or the foam cells including so-called Touton giant cells which makes the pathologic picture distinctive from other forms of xanthoma. There is spontaneous involution of the lesions within six months to three years. Polano justly has objected to the term *nevoxantho-endothelioma* because the condition is not a true endothelioma and he has suggested the term *xanthelasma naeviforme* which I would modify to the term *xanthomatosis naeviforme* because in this country, as contrasted to European literature, the term *xanthelasma* has been used to designate xanthelasma palpebrarum or xanthomas of the eyelids alone.

Juvenile xanthoma.^{12, 13, 16}—Juvenile xanthoma usually presents features of ordinary xanthoma tuberosum, occasionally of xanthoma disseminatum. At times, there are combinations of both types of lesions with or without evidence of Hand-Schüller-Christian disease. There is a marked hereditary

tendency^{15, 16} including very frequent occurrence of severe cardiovascular disease, rarely of hepatosplenomegaly with features of both tuberosa and disseminate types of xanthoma. Xanthomatous involvement of the mitral valves and myocardium has frequently been described but typical cases of angina pectoris and coronary sclerosis with the diagnosis confirmed by postmortem examination have been reported. A

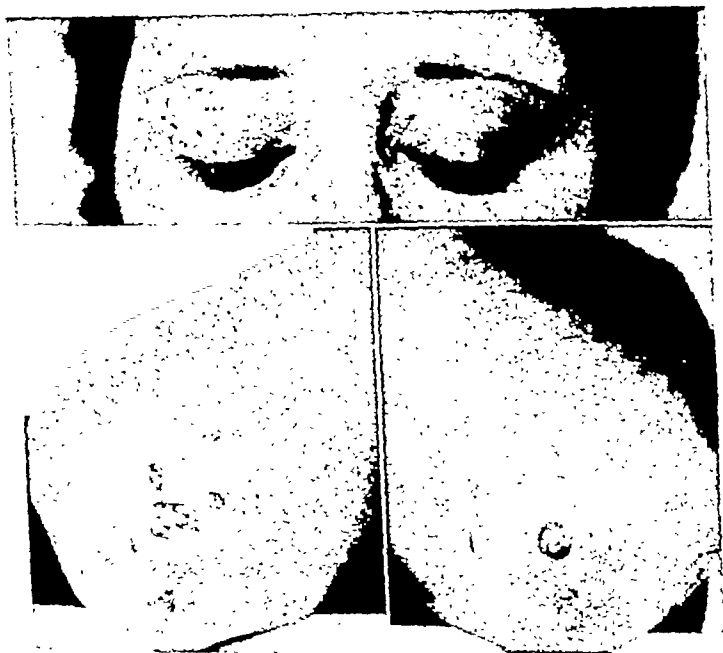


Fig. 155.—Typical lesions of xanthoma tuberosum on elbows and xanthelasma of eyelids; the patient had obstructive jaundice, secondary biliary cirrhosis and hyperlipemia.

definite hyperlipemia and hypercholesterolemia is usually present. The prognosis of juvenile xanthoma must be guarded because of the frequent and serious systemic manifestations associated with the disease.

Xanthoma tuberosum.—This type¹⁵ which is the most common is characterized by xanthomatous yellowish to brown nodules, papules or plaques that predominate on the extensor surfaces (Fig. 155), including involvement of the tendon

sheaths. Histologically, there are typical foam cells and Touton giant cells which later are characterized by the arrangement of their nuclei in a complete circle surrounded by deposits of lipoids in the cytoplasm. There is a definite hyperlipemia and usually an increase in cholesterol in both the blood and the cutaneous lesions. In about 40 per cent of sixty-five cases studied, there is associated angina pectoris or coronary sclerosis or occlusive vascular disease of the extremities with intermittent claudication in the form of arteriosclerosis obliterans. The age incidence as compared with the original report by Osterberg and me¹⁵ remains at less than fifty years of age with a high incidence of females and relative absence of Jewish patients.

Müller has emphasized that hereditary heart disease due to xanthomatosis is fairly common and that the syndrome of cutaneous xanthoma, hypercholesterolemia and angina pectoris presents itself as a well-defined disease entity in the first, second, third and fourth generations and that it is a dominant hereditary disease. Polano also has confirmed the frequent incidence of cardiovascular disease in xanthoma tuberosum. Barker has emphasized the increase in plasma lipoids in 73 per cent of cases of arteriosclerosis obliterans, three of which were associated with xanthoma tuberosum of the skin and that thrombo-angiitis obliterans (Buerger's disease) on the other hand, is associated with essentially normal blood plasma lipoids. Recent articles indicate that many cases of coronary sclerosis are associated with hyperlipemia and hypercholesterolemia independent of familial history or evidence of cutaneous xanthomatosis.^{1, 15, 19, 23, 26} Hyperlipemia, however, does not necessarily imply cardiovascular disease, nor is angina pectoris always associated with hyperlipemia and hypercholesterolemia. The aforementioned findings indicate, however, that hyperlipemia and hypercholesterolemia play an important etiologic rôle in some types of arteriosclerosis.

Lesions of xanthoma tuberosum may involute partially or spontaneously following a low-fat or particularly an animal-fat free diet and the blood lipoids can be brought down to approximately normal values by such a diet. Occasionally, small doses of thyroid extract are indicated.¹⁸ Good results have recently been reported from the use of Dragstedt's pancreatic

hormone, lipocaic, which Broun, Huber and Casey gave successfully to prevent development of arteriosclerosis in rabbits to which they were feeding a high-cholesterol diet.¹² Further studies are necessary along these lines and also in regard to the effect of choline on xanthomas.

Under xanthoma tuberosum must be included xanthomas of the tendon sheaths and synovial membranes.⁵ Again, there usually is a hyperlipemia and hypercholesterolemia. When the joints are involved aspiration of the joints reveals a bloody fluid, often with increase of cholesterol. Extracellular cholesterosis of Urbach^{10, 15} probably represents a fibrous type of xanthoma tuberosum in which there may or may not be mild hyperlipemia and a few foam or xanthoma cells can still be recognized. The presence of the increased free cholesterol in the cutaneous lesions is of doubtful significance as this frequently occurs in any fibrous stage of xanthoma.¹⁴ A form of xanthoma of the central nervous system with degenerative changes in speech, ataxia and atrophy of the muscles in relation to xanthoma of the tendons and xanthoma tuberosum has recently been described by von Bogaert and his associates. Finally, it must be mentioned that xanthoma tuberosum may occur in association with disease of the liver or with diabetes.

Xanthoma disseminatum.—It is fundamentally important to distinguish xanthoma disseminatum (Fig. 156) from xanthoma tuberosum.^{13, 15, 18} Xanthoma disseminatum is characterized by fine papules and plaques predominating on flexor surfaces, especially the axillary folds and also involving the mucous membranes including the pharynx and larynx, which often necessitates tracheotomy. Frequently there is involvement of the pituitary region with an associated mild diabetes insipidus. The blood lipoids are normal or even subnormal in concentration whereas the histologic picture is the same as that in cases of xanthoma tuberosum and is a typical picture of xanthoma, including increase in cholesterol and especially cholesterol esters in the tissues. In none of the cases in this group have there been signs of Hand-Schüller-Christian disease except for the diabetes insipidus. There is no cardiovascular disease. The patients showed no response to any type of diet, roentgen therapy or medication with thyroid or insulin. As a rule, there is gradual progression of the disease, occasionally with terminal

involvement of the liver and death from inanition or intercurrent infection.

Xanthelasma of the eyelids.—The condition may be seen in many types of cases of xanthoma especially in association

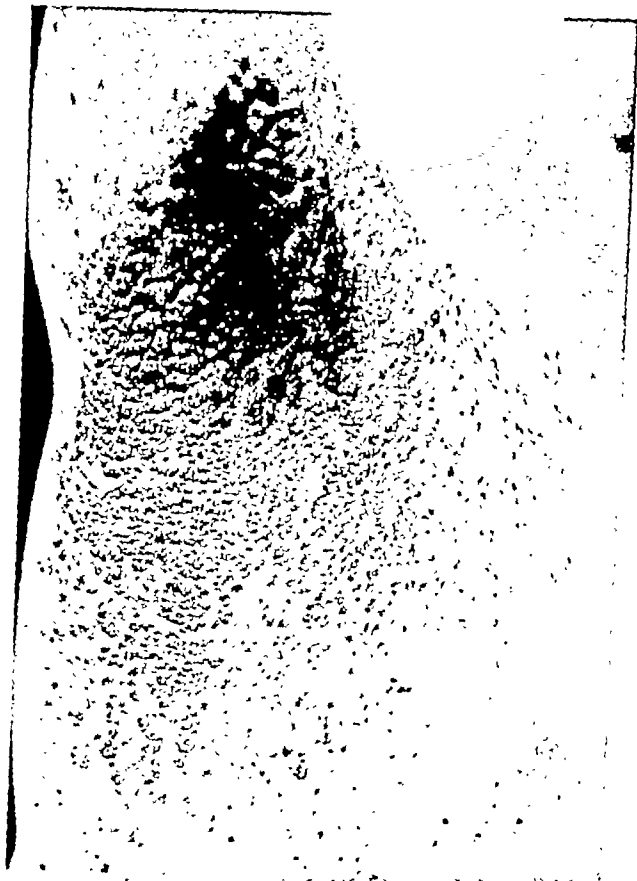


Fig. 156.—Characteristic appearance and distribution of lesions of xanthoma disseminatum on flexor surface of axilla. The patient had involvement of the trachea and larynx which necessitated tracheotomy. He also had symptoms of diabetes insipidus.

with xanthoma tuberosum or xanthoma disseminatum. Xanthelasma confined to the eyelids alone is much more frequently encountered than any other type of xanthoma. Nevertheless,

in about 70 per cent of these cases a moderate to marked elevation of blood lipoids or disturbance in ratio between various lipoids occurs. Out of the last forty cases of xanthelasma limited to the eyelids alone which I studied (previously unpublished data), the blood lipoids were normal or only slightly elevated in twenty and in twenty there was marked elevation of the cholesterol, lecithin and total lipoids without disturbance of the cholesterol-cholesterol ester ratio. In all the latter twenty cases there was evidence either of angina pectoris, intermittent claudication and occlusive vascular disease of the extremities or a severe degree of hypertension and arteriosclerosis. The incidence of cardiovascular disease as a whole, however, in cases of xanthelasma of the eyelids is probably between 30 and 40 per cent and is usually seen in later decades of life whereas in a considerable percentage of cases, severe cardiovascular disease developed in the early forties which was a striking feature of the cases of xanthoma tuberosum. The histopathologic picture of xanthelasma of the eyelids is typical for xanthoma except that there are relatively few Touton giant cells. It is not a degenerative process of the muscles of the eyelids as was formerly thought. Involution of lesions of xanthelasma may occur following the giving of a diet free of animal fats. Further observations are necessary to evaluate this method of treatment. Surgical excision when the lesions are large seems to be the method of choice but recurrences are not infrequent. Xanthelasma of the eyelids should not be regarded as a local benign cutaneous xanthoma because of its frequent association with systemic xanthomatosis.

Xanthoma diabetorum.—This is characterized by multiple small yellow to brown, discrete to confluent plaques on the extensor surfaces with predilection for the palms and soles. There may be marked pruritus with resultant secondary excoriations (the so-called *secondary xanthomatosis* of Thannhauser and Magendantz). It is essentially xanthoma tuberosum occurring in patients with severe diabetes who have marked hyperlipemia. Cases reported in the literature of typical xanthoma tuberosum associated with mild diabetes probably should not be classified with xanthoma diabetorum.²⁵ The lesions involute promptly under a proper dietary regimen plus the use of insulin. The fatty acids are greatly increased over choles-

terol which, however, is also markedly elevated. The fatty acids in the blood respond much more promptly to treatment than does the cholesterol. Involuting lesions reveal extracellular as well as intracellular deposits of lipoids outlining the reticulo-endothelial system.

Necrobiosis lipoidica diabetorum.⁸—This is characterized by multiple colored plaques that vary in size and occur chiefly on the extremities, especially on the legs; they may be unilateral or bilateral and frequently develop following trauma. Ninety per cent of the cases are associated with diabetes and 90 per cent occur in females. In 18 per cent of a series of eighty-six cases described in the literature, cutaneous lesions of *necrobiosis lipoidica diabetorum* appeared from one to five years before any symptoms of diabetes mellitus. Generally, symptoms of diabetes have preceded the cutaneous lesions. In 10 per cent of cases of *necrobiosis* in which evidence of diabetes was not demonstrated, the majority of patients gave a history of familial incidence of diabetes or of abnormal sugar tolerance curves. The blood lipoids were normal in the non-diabetic individuals and usually so in cases associated with diabetes mellitus, or elevation of the lipoids is consistent with the relatively severe degree of usually poorly controlled diabetes that is encountered in most of these cases. The histopathologic picture is characterized by regions of central pseudonecrosis of the connective tissues with extracellular deposits of lipoids, usually with an excess of free cholesterol or lecithin in the tissues. The condition is not to be confused with discrete solitary or multiple regions of diabetic gangrene which neither show the clinical picture nor the characteristic histologic picture of *necrobiosis*. The histologic picture of *necrobiosis lipoidica diabetorum* may need to be distinguished from *granuloma annulare* by staining for fats. Little success has been reported regarding treatment of the lesions of *necrobiosis*. Most recently, the use of repeated exposures to ultraviolet light has been advocated.

Lipoid proteinose (Urbach).—Lipoid proteinose (Urbach) is a rare condition; usually it occurs in infancy or childhood but it may develop first in adult life.¹⁴ There is a hereditary tendency and also a familial tendency toward diabetes. Nodular and hyperkeratotic, verrucous and fibrous sclerosing

lesions predominate on the face, extremities and mucous membranes including the larynx and pharynx. Tracheotomy may be necessary. The total concentration of blood plasma lipoids is usually within normal limits but there frequently is a tremendous disproportionate increase in the lecithin. Histologically, there is an increase in lecithin and in free cholesterol which occurs as extracellular deposits of lipoids around the blood vessels and in the form of homogeneous diffuse infiltration with lipoids in masses of connective tissue. Involvement of the pharynx and larynx must be distinguished from that seen in cases of xanthoma disseminatum in which there is disturbance of cholesterol rather than of phosphatide metabolism and in which there are typical foam cells which are not present in lipid proteinose. The cutaneous lesions fail to present any yellow or xanthomatous hue. The condition probably falls between Niemann-Pick disease and hepatosplenomegaly of Bürger and Grütz in that it has to do with disturbance of phosphatides. There is no satisfactory treatment known and many of the cases have terminated fatally.

Xanthoma in relation to disease of the liver.—Cutaneous xanthoma in relation to hepatic disease is usually secondary to the hepatic involvement but may be primary.¹² Usually, one sees discrete lesions of xanthoma tuberosum. Occasionally combinations of xanthoma tuberosum and xanthoma disseminatum occur, especially in children, or xanthoma disseminatum occurs alone in the terminal stages of that type of xanthoma.^{12, 15} There is a predilection for lesions to occur on the palms and soles which is also seen in cases of xanthoma diabeticorum. There is usually a hyperlipemia but usually without relative increase in free cholesterol as has previously been reported in regard to xanthomatous involvement of the liver as a whole. Secondary xanthomatosis of the skin, following obstructive jaundice associated with stricture of the common duct is the most common type. A relatively rare condition is that described by Bürger and Grütz of hepatosplenomegaly, lesions of the skin and mucous membranes and marked increase in phosphatides and free cholesterol in the blood and tissues.¹² This may occur in childhood or in adult life. Typical foam cells are seen histologically. The lesions on the mucous membranes rarely are extensive enough to necessitate tracheotomy.

Again, the disturbance of phosphatides would group this type with Niemann-Pick disease on the one hand and with lipoid proteinose on the other. Some response has been noted in the few cases reported to dietary measures including low-fat and animal-fat free diets.

Xanthoma in relation to tumors.—It is to be emphasized that so-called xanthic tumors of the tendon sheaths or xanthomas of the tendon sheaths and synovial membranes are essentially types of xanthoma tuberosum in that they occur on the extensor surfaces and are associated with hyperlipemia. Malignant changes do not occur.⁵ Xanthic changes are frequently seen in true malignant neoplasms of various types; usually these xanthic changes represent various phases of lipoid degeneration of tumor cells or tissues being invaded by tumor cells. These can be distinguished by concomitant histopathologic findings. An increase in cholesterol in malignant neoplasms may occur with or without a decrease in the phosphatides. Experimentally, an increase in cholesterol may stimulate growth of neoplasms in animals.

DIFFERENTIAL DIAGNOSIS

Besides the types of cutaneous xanthoma just mentioned, there is multiple cholesteatoma of rare occurrence, also so-called lipoid tophi⁷ that resemble gouty tophi and finally atypical cases of cutaneous xanthoma which cannot early in the course of the disease be accurately classified.¹⁶ In distinguishing between cutaneous lesions of most types of xanthoma, one must consider the so-called yellowing dermatosis of Weidman including senile elastosis (fatty degeneration of elastic tissues) and dermatoses independent of the xanthomatosis that are associated with xanthochromia and carotinemia. Pseudoxanthoma elasticum, urticaria pigmentosa, multiple ganglioneuromas of the skin and Danlos' syndrome may simulate the clinical appearance of cutaneous xanthomas but can be distinguished from the aforementioned conditions by concomitant findings and entirely different histologic pictures. Solitary or multiple lesions of histiocytoma (dermatofibroma) may closely simulate the clinical and histologic picture of solitary lesions of xanthoma tuberosum in a fibrous or involuting stage. In cases

of histiocytoma, hyperlipemia may be present and a final distinction between the two conditions cannot always be made.

In both the fibrous stage of ordinary xanthoma and certain types of histiocytoma (dermatofibroma lenticulare), one encounters deposits of hemosiderin as well as lipoids and even an increase in melanin pigmentation of the epidermis so that clinically the lesions may be suggestive of a deeply seated pigmented nevus. Foot has described a case which clinically simulated a case of pigmented nevus in which he found increase in nerve fibers. He advanced the concept of a relationship between certain types of primary cutaneous xanthomas, neurogenic sarcomas and melanoma. However, all these conditions frequently show an increase in argentophilic fibers including *Gitterfasern* or lattice fibers and which at times may be indistinguishable morphologically from nonmedullated nerve fibers. Foot's case would seem to fit in with what dermatologists call a histiocytoma that possibly was undergoing a change to dermatofibrosarcoma protuberans of Darier. True xanthomas, in spite of a few articles in the literature to the contrary, do not, I believe, undergo malignant change. I can see no reason to relate xanthomas to melanomas and have not found any increase in sheaths of Schwann or nerve trunks with special silver stains in the true xanthomas that I have studied.

ETIOLOGY

No one etiologic concept explains the multiple manifestations of various cutaneous and systemic types of xanthomatosis. The interrelation of multiple known and unknown factors of lipid metabolism which have been mentioned previously would support this view. The liver apparently plays a definite rôle in the synthesis of phosphatides and sterols. It is possible that the presence of hormones in the pituitary gland is a factor in xanthoma disseminatum and Hand-Schüller-Christian disease just as diseases of the liver and spleen may be factors in other types of xanthomatosis. The gallbladder, however, according to recent investigation plays a very minor rôle in regard to lipid metabolism and would appear to have little significance in regard to xanthomatosis. Hormones from the pancreas, sex organs and the thyroid gland together with disturb-

ances or deficiencies of various vitamins are closely linked with disturbances in lipid metabolism and xanthomatosis. A great many explanations have been offered for xanthomatosis, of which only a few of the more prominent ones will be mentioned.

Thannhauser and Magendantz expressed the belief that the cells of the reticulo-endothelial system (foam or xanthoma cells) actually produce various lipoids and thus these authors suggested the existence of a primary essential xanthomatosis, including (1) metaplastic reticular cholesterosis, which applies to most types of cutaneous xanthoma and to Hand-Schüller-Christian disease; (2) metaplastic cerebrosidosis for Gaucher's disease and (3) metaplastic sphingomyelinosis for Niemann-Pick disease. They then recognized a secondary type of xanthomatosis due to lipemia, in which the foam cells simply store the excess lipoids (xanthoma diabeticorum an example), and finally, localized formation of xanthoma cells in true tumors. It is difficult to conceive that the few cutaneous lesions in some cases of xanthoma tuberosum in which there is a marked hyperlipemia, and in which there is no systemic manifestation, can be responsible for the hyperlipemia. This would be equivalent to explaining an increase in the uric acid of the blood as the result of gouty tophi. Xanthomatous tumors have no histologic features of true neoplasms. Hypercholesterolemia and hyperlipemia may be seen in myxedema and many other conditions without evidence ever having been offered of any increase in histiocytes or reticulo-endothelial cells in the skin or internal organs.

Siemens' and also Polano's concept of cholesterophilia or a special affinity of cells for cholesterol would explain the normal blood lipoids seen in disseminate forms of xanthomatosis.

Bloch and Shaaf explained xanthoma on the basis of an imbalance between the various lipoids;^{12, 13, 15, 18} they emphasized a disturbance in the cholesterol-phospholipid ratio. Studies at The Mayo Clinic do not point to significant changes in this regard in most types of xanthomatosis.

Cutaneous xanthomas have been said to be produced as result of trauma and local irritation. These factors play a minor rôle in most types of xanthomatosis.

Weidman wrote of involvement of cells of cutaneous nerve sheaths as a factor in the production of lipoids in certain types